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THE MONTH

The Symposium

WHAT Dr. Kenneth Smith describes in his introductory article to our symposium on 'Virus Diseases' this month as 'the epic of virus research' is one of the great success stories of medical research. In view of what we now know about the chemical constitution and structure of viruses, it is almost incredible that little over a quarter of a century ago a leading authority on the subject could, to quote Dr. Smith, 'remark with some justification that the size and shape of no viruses were known'. Two major factors have been responsible for the phenomenal progress that has been achieved during the last two decades. One is the introduction of tissue culture; the other is the electron microscope. So rapid has been the progress in the research field that today the clinician is being presented with what can only be described as an embarrassment of viruses. So many are being discovered that it is impossible for the clinician to keep pace with them and correlate them with specific diseases. Fortunately, the practical implications of these discoveries have not been overlooked, and Dr. Isaacs' article on 'Interferon: The Prospects', which concludes our symposium, raises the intriguing possibility of a wide-spectrum viral antibiotic.

After the Election

ALTHOUGH there will be general relief among doctors that Mr. Macmillan is to remain at the helm of State, the return of the Conservative Party to power does not mean that the medico-political barometer is 'set fair'. As *The Times* pointed out during the general election, 'Labour and Conservative policies differ about the pace of development of the health service, not about its direction . . . Nine-tenths of the Labour executive's recent catalogue of improvements for the health service would not provoke Conservative dissent'. This is a point which is too often overlooked by the profession—especially those who are members of the Conservative Party. We all know that the aim of the Labour Party is a whole-time medical service and a nationalized pharmaceutical industry. So far as the former is concerned, however, is there any difference between the two Parties except the speed with which this is to be achieved?

The record of the Conservative Party's last two periods in power suggests that no such difference exists. The one ray of hope is that the more forward-looking younger section of the Party, which constitutes what is known as the Bow Group, is showing healthy signs of discontent. According to the

autumn issue of their quarterly journal, *Crossbow*, which was published just before the Election, what is required is 'nothing less than that the Health Service should be removed from direct governmental control, that responsibility for its central organization and administration should be removed from the Ministry of Health and an independent body set up to manage its affairs'. What is required, according to the Group, is an administration 'whose first object is the maintenance of the health of the nation and not the observance of civil service bumbledom'. 'A government department', it contends, 'may be the right body to organize guns or roads, but a nation's health is not so amenable to minutes and Ministerial dicta'. On the well-proven medical principle that where there is life there is hope, the outlook for the future is not entirely bleak so long as constructive ideas such as these are fermenting among the future leaders of the Conservative Party.

Collegiate Caution

DISAPPOINTING though it must have been to its members, the decision of the council of the College of General Practitioners to abandon its plans for erecting a large building in Lincoln's Inn Fields is a wise one. Indeed, it sets an example which should give the three 'Royal' colleges 'furiously to think'. Since the end of the 1939-45 War the surgeons, obstetricians, and physicians have embarked upon grandiose building schemes which reflect more credit upon their hearts than upon their heads. In the case of each of them three primary considerations would appear to have been ignored.

The first is the very elementary one that the bigger and more elaborate the building the greater the cost of maintenance. Large though it may be, the initial capital expenditure is a minor financial consideration compared with the capital required to produce the annual income necessary for maintenance, and the methods of publicity to which one of the Royal Colleges has already had to resort are scarcely in keeping with the traditions of what some of us still look upon as a learned profession. The second consideration is that there are already sufficient universities and medical schools with facilities for research and that, if the large sums being spent on the modern equivalents of bricks and mortar had been spent on endowing research departments already in existence, a much larger proportion of it could have been spent on actual research activities. The third consideration is that these grandiloquent schemes are absorbing a great deal of energy which would be much better expended on looking after and advancing the interests of the members and fellows of the colleges concerned. Finally, the insular policies of the three colleges—particularly the two senior ones—has killed once and for all the concept of an Academy of Medicine which seemed so near fruition in those halcyon days of planning that immediately followed the termination of hostilities in 1945. The concept was a noble one—an Academy of Medicine in Lincoln's Inn Fields that would have housed the three Royal Colleges, and now the College of General Practitioners. Its foundering on interprofessional jealousies is one of the major tragedies of post-war medicine in this country.

'IT is a rule without any exception, that no patient ought ever to stay longer in hospital than is absolutely essential for medical or surgical treatment . . . Every hospital should have its convalescent branch'. So said Florence Nightingale nearly a century ago. Unfortunately, as the working party, appointed by the Minister of Health to examine the provision of convalescent homes in the London area, point out in their recently published report ('Convalescent Treatment'. H.M. Stationery Office, price 3*s*.), 'the treatment of convalescence has remained a medical and nursing backwater, largely unaffected by changes in the main stream'. There is no real shortage of convalescent-home beds (in the London area there are around 6,500, which gives a ratio of 1 to 13 hospital beds), but they are not being put to the best use.

Convalescent Treatment

According to the working party's report, 'for a majority of those who now receive it and for some who do not, convalescent treatment requires a "new look" in accordance with modern concepts. It needs to become more active, more planned and more integrated with other aspects and disciplines of medicine'. 'Medically', it is rightly pointed out, 'the proportion of cases in which a period of passive convalescence is essential has greatly diminished', and such convalescence has 'become to a much greater degree, "a pleasant convenience to the patient or a thoughtful gesture by the referring physician" '. What is now required is 'a more vigorous attack along the lines of rehabilitation for the sick similar to that developed in rehabilitation for the disabled', carried out in conjunction with research into the problems of convalescence'. In this connexion one of the most interesting recommendations of the working party is that there should be an investigation into the possibility of using convalescent homes for the prevention of disease or 'the preparation of patients in sub-standard health before surgical operations'. Equally important is the recommendation for the 'experimental provision of Day Convalescent Centres based on the Department of Physical Medicine at general hospitals in large centres of population'.

AN investigation by P. W. Bothwell (*Med. Offr*, 1959, **102**, 125) into the smoking habits of 8,314 school children (4,270 boys and 4,044 girls) in secondary modern, grammar, and technical schools in Oxfordshire throws an interesting light on the extent of this habit in the rising generation. Although the minimum level of smoking for the purpose of this study was as low as 'at least one cigarette a week', only 33.2 per cent. of the boys had never smoked at all; the corresponding figure for girls was 68.5 per cent. At all ages boys smoked more than girls. Only 8.5 per cent. of the latter exceeded five a week, whereas 22.9 per cent. of boys smoked over ten a week, and 1.8 per cent. smoked between 50 and 75 a week. The value of cigarettes smoked was £4,350 a year.

Cigarettes and Children

From the point of view of planning propaganda to discourage smoking this study brings out several important points. In the first place, among boys there were two definite periods for the age at which smoking was started—

10 years and again at 13 and 14 years. For girls the most common ages for starting were 13 and 14 years. The most frequent sources of supply of cigarettes were shops and 'friends': 56.4 per cent. of the girls obtained their supply from this latter source. Slot machines accounted for 11.2 per cent. of boys' cigarettes and 4.5 per cent. of girls'. Smoking in the home accounted for 27.4 per cent., and smoking in cinemas for 32.7 per cent., of the total incidence. Over 50 per cent. of the boys, and 45 per cent. of the girls, smoked with parental knowledge. Finally, there was a close correlation between the smoking habits of children and that of the parents—especially the mother. When only the father smoked, the probability of the children smoking was little different from that when neither parent smoked, but when both parents, or the mother alone smoked, the probability of the child smoking was significantly greater than when neither parent smoked or when the father only smoked. Equally indicative of the importance of parental habit is the fact that in only 20 per cent. of the families included in the study did neither parent smoke.

The Artist and His Eyes

WHAT has been the influence of eye disease in the artist on the great pictures of the world? To what extent was the relatively high incidence of myopia among the early French impressionists responsible for the introduction of impressionism in art? These are but two of the fascinating problems discussed by P. D. Trevor-Roper in a paper on 'The influence of eye disease in pictorial art' which he read before the section of ophthalmology of the Royal Society of Medicine (*Proc. Roy. Soc. Med.*, 1959, **52**, 721). As he points out, 'the diseases that have beset the great men of history have always invited speculation' and, certainly so far as the eyes of artists are concerned, much of this speculation will not stand up to critical examination. Of the four major eye diseases that he discusses, however, two—myopia and colour blindness—he considers 'could have an undesirable effect on the artists' rendering'.

Beyond the farthest point of his natural focus the vision of the myopic artist becomes a sort of 'peripheral vision' such as the normal person sees out of the corner of his eye, with a loss of detail and a relative clarity only of the essential lines and contours. Although there is no definite evidence that Monet, who, to quote Roper, 'so pioneered the cultivation of this peripheral type of vision', was myopic, Cézanne and Degas both were. Indeed, because of his failing vision, the latter was reduced to painting in pastel rather than oil. Gordon Craig was also grossly myopic, and Roper puts forward the tempting thesis that 'it may well have been partly as a result of this myopia that he pioneered the new approach to stage-designing, and persuaded his followers [notably Reinhardt] of the proper supremacy of colour and form over detractory details'. So far as colour-blindness is concerned, the most interesting point raised by Roper is the possibility that Constable was partially red-green colour-blind. In support of this suggestion he notes the 'brown mantle that characteristically covers his spring trees'.

THE NATURE OF VIRUSES

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For many years after the discovery of the first virus, one affecting a plant and causing the disease of tobacco mosaic (Iwanowski, 1892), progress in the study of these agents was very slow. Learned discussions were held upon such subjects as 'are viruses particulate?', although no-one suggested what they could be if they were not particulate and, as lately as 1932, Rivers remarked with some justification that the size and shape of no viruses were known.

THE VERSATILITY OF VIRUSES

The isolation of the tobacco mosaic virus by Stanley (1935) enabled us to visualize a virus as a definite entity and this was the first step in a long series of spectacular advances which make up the epic of virus research during the last two decades.

In 1915, Twort made the important discovery that some agent had the power of dissolving or lysing bacteria; about the same time a Canadian worker (d'Herelle, 1917) made the same discovery and so for a time it was known as the 'Twort-d'Herelle phenomenon'. The bacterium eaters, or 'bacteriophages' as d'Herelle called these bacterial viruses, have been studied almost more intensively than any other virus and much information on their structure and mode of multiplication has been obtained.

Besides bacteria, flowering plants, and the higher animals, viruses attack almost every other type of living organism including insects, fish, frogs and —the latest discovery—those minute pests of plants known as red spiders or spider mites which belong to the order *Arachnida*. Under the electron microscope many of the small viruses, although coming from such disparate hosts, look very much alike and a plant virus causing a disease known as turnip yellow mosaic is, as we shall see, remarkably similar in structure and external appearance to the virus of poliomyelitis.

The methods of dissemination of viruses are as varied as their hosts and, whilst some are spread on fomites, many require an intermediary to act as vector. These vectors may be dogs or bats in the case of rabies, mosquitoes for yellow fever or equine encephalomyelitis, and many different types of plant-feeding insects for the plant viruses. In addition, some plant viruses are spread by mites, and even by nematode worms, whilst Shope (1941) has shown that the earthworm and the pig lungworm play an essential part in the cycle of infection with the swine influenza virus. A further instance of the versatility of these agents is the ability of some plant viruses to multiply both in their insect vectors and in the plant hosts, thus giving rise to doubt as to whether they are plant or animal viruses.

SHAPE AND STRUCTURE OF VIRUS PARTICLES

The virus of tobacco mosaic, the first virus to be discovered, the first to be isolated in large amounts and the first to be seen on the electron microscope, was also the first to have its shape and structure definitely established. In 1933, two American workers (Takahashi and Rawlings, 1933) noticed that when sap from a mosaic-diseased tobacco plant was made to flow, and was observed by polarized light, it showed the optical phenomenon of double refraction which indicated that it contained rod-like entities. This observation was amply confirmed later on by the electron microscope which showed the virus to be a rigid rod measuring 350×15 mμ (1 mμ equals one-millionth of a millimetre) (fig. 1). A characteristic of the smaller viruses is their extreme uniformity of size; this expresses itself in ability to form crystals in which all the particles are pointing the same way and are identically situated. This extreme uniformity of size makes viruses useful for physical studies.

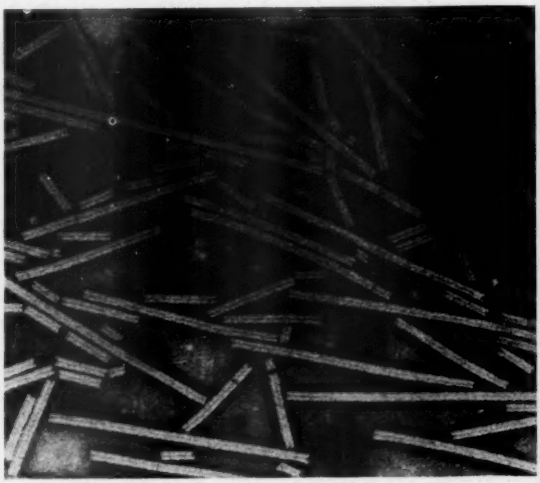


FIG. 1.—Tobacco mosaic virus particles stained with phosphotungstic acid; note the hollow centre picked out by the stain. (x 120,000.)

There are four main methods for studying virus size and structure: by chemical analysis, by hydrodynamic methods, by x-ray crystallography and by electron microscopy. It is with the last two that we are concerned here. By means of the electron microscope the size and shape of virus particles are easily determined and special staining methods can delineate details of surface structure. Improvements in technique make it possible to cut ultra-thin sections of virus particles and this, combined with the special staining methods, shows some of the internal structure.

Tobacco mosaic virus.—So far as detailed surface structure of the tobacco mosaic virus (TMV) particle is concerned the results of high resolution electron microscopy have been rather disappointing although some of the new staining methods promise better results. Most of the information therefore is derived from x-ray studies. We know that the smaller viruses consist of two distinct and separable parts, the protein and the nucleic acid, ribonucleic acid (RNA) in the case of the plant viruses and RNA or some-

times deoxyribonucleic acid (DNA) in the case of the animal viruses. We have now to see how the protein and the RNA are put together to form the rod of TMV.

It was first suggested by Bernal and Fankuchen (1941), on the results of their x-ray studies, that the protein of TMV was built up of sub-units and this was further indicated by end-group analyses carried out by Harris and Knight (1952) and others. In 1954, Watson showed by means of x-ray diffraction that the structural sub-units of the particle form a helix, and more recent work by Franklin and her co-workers (1957), using TMV to which atoms of mercury had been attached, have suggested that there are 49 sub-units on three turns of the helix. This gives a total of 2,130 sub-units in a complete rod, compared with 2,900 repeating sub-units, of molecular weight about 17,000, calculated by chemical methods (Knight, 1957).

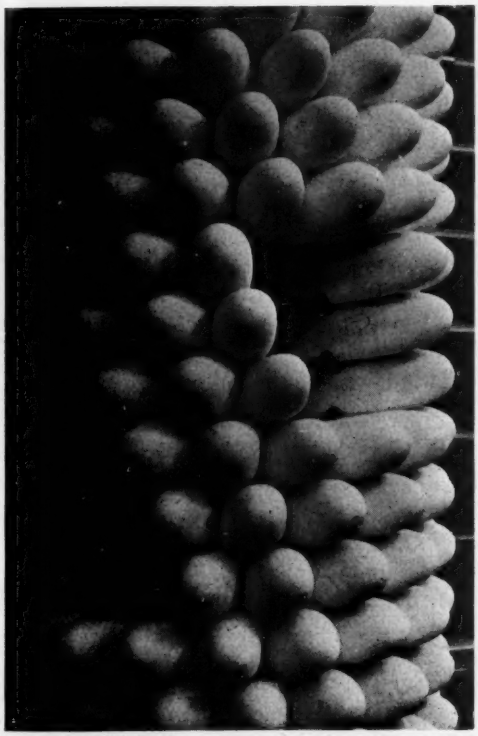


FIG. 2.—Model of a tobacco mosaic virus particle, showing the protein sub-units set in a helix; some of the sub-units have been removed to show the strands of RNA. (After Franklin and Klug.)

The RNA is thought to be only 6 per cent. of the particle and appears to be all in one piece, a single strand polymer following the pitch of the helix. Hart (1955) showed that it was possible to remove part of the protein coat from the TMV particle leaving the RNA protruding and apparently intact and further that this RNA could be covered up again when more TMV protein was supplied. This suggests that the RNA does not run through individual protein sub-units, but rather that the sub-units pack together in such a way as to leave space for the RNA between them. In fig. 2 is a model of the TMV particle based on the results of x-ray studies by Franklin and her colleagues. Some of the protein sub-units have been removed to show the suspected position of the RNA in relation to them.

Poliomyelitis virus.—In 1956 it was suggested by Crick and Watson that all small viruses are built up on a framework of identical protein sub-units packed together in a regular manner. They showed that three types of symmetry were possible: tetrahedral, octahedral and icosahedral. Shortly after this it was proved by x-ray crystallographic studies (Caspar, 1956; Klug *et al.*, 1957a, b) that two very small plant viruses, those of turnip yellow mosaic and tomato bushy stunt, possessed the characteristics of icosahedral symmetry. Now similar studies have been carried out by Finch and Klug (1959) on crystals of poliomyelitis virus provided by Schaffer and Schwerdt in California. Although there is still some doubt as to the precise way in which the sub-units are arranged to form the spherical shell of the virus, the ratio of the particle size to the distance between the sub-units indicates that the sub-units in the shell are packed very compactly so that each has at least four, and probably five, neighbours in contact with it. The arrangement is probably similar to that suggested by Klug and his co-workers for the virus of turnip yellow mosaic, and is shown in fig. 3.

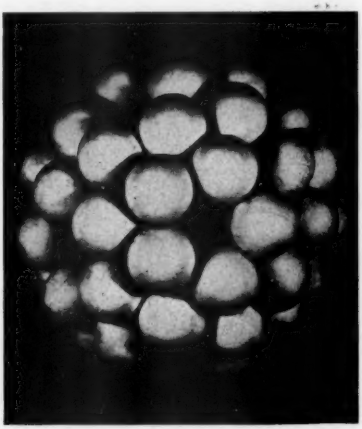
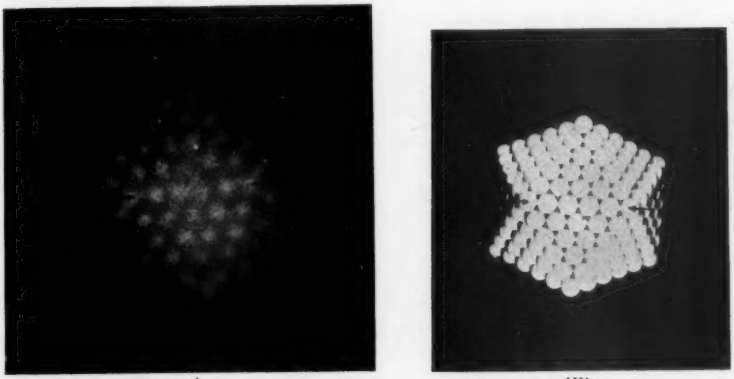


FIG. 3.—Schematic model of a likely arrangement of the sixty identical structural sub-units forming the protein shell of the poliovirus particle. The actual appearance of the virus particle will depend upon the precise arrangement adopted and on the shape of the sub-unit which are not known. The diameter of a sub-unit is about 60 to 65Å. (After Finch and Klug, 1959.)

It seems therefore that the poliomyelitis virus is built up out of sixty identical or structurally similar protein sub-units. About 25 to 30 per cent. of the particle is RNA, but there is no very direct x-ray evidence as to the position of the nucleic acid in the particle. By analogy with the virus particle of turnip yellow mosaic, however, we might conclude that it forms the centre of the protein shell (Markham, 1951).

Adenovirus and herpes virus.—We have seen how it is possible by means of x-ray crystallographic studies to obtain accurate pictures of the architecture of some viruses. It is also possible now to obtain a direct visual image of certain viruses on the electron microscope using a special staining technique which delineates the protein sub-units. The stain used is a 2 per cent. solution of phosphotungstic acid adjusted to pH 7.4 (Brenner and Horne, 1959). An electron microscopical study, using this technique, has been made of adenovirus and the virus of herpes (Horne *et al.*, 1959). The nature of the arrangement of the protein sub-units can easily be deduced from the micrograph reproduced in fig. 4 (A). The particle has a roughly

hexagonal outline and is clearly faceted, each facet being an equilateral triangle with a side consisting of six sub-units. The presence of triangular facets excludes a dodecahedral form and suggests that the particle is an icosahedron. A model of an icosahedron with a side of six sub-units has been



(A) (B)

FIG. 4.—(A) Adenovirus particle at high magnification (x 450,000). Note that the sub-units have a definite pattern. (B) Photograph of a model of an icosahedron in same orientation. The arrows mark sub-units which lie on five-fold rotational symmetry axes. (After Horne *et al.*, 1959.)

built from table-tennis balls and fig. 4 (B) is a photograph of this model standing on an edge. The arrangement of the sub-units in the virus particle and in the model are identical.

Herpes virus shows a similar sub-unit structure but the sub-units appear to be hollow and ring-shaped when compared with adenovirus (fig. 5).

FIG. 5.—Herpes virus particle showing the hollow sub-units. (x 300,000.) (After Horne *et al.*, 1959.)

Tipula iridescent virus.—Before concluding this discussion of the architecture of viruses, it may be of interest to describe briefly another technique on the electron microscope from which the shape of a virus particle can be deduced. The *Tipula* iridescent virus (TIV), which was found infecting the larva of a fly *Tipula paludosa*, has a comparatively large and extremely uniform particle measuring 130 mμ. It gets its name from the fact that it forms crystals showing a brilliant iridescence, and these iridescent crystals actually occur in the body of the living infected insect. By using a technique

of double shadowing, Williams and Smith (1958) were able to demonstrate unequivocally that the virus particle was an icosahedron. In figure 6 is shown a model of an icosahedron, shadowed by two light sources separated 60° in azimuth and orientated so that an apex of the hexagonal contour points directly towards each light source. Note the shape of the two shadows, one has five sides and is blunt-ended and the other has four sides and is sharp-ended. In figure 7 is an electron micrograph of a frozen-dried particle of TIV which has been shadowed similarly to the model; note the identical appearance of the shadows.

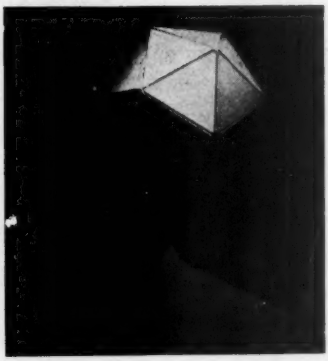


FIG. 6.—A model of an icosahedron, shadowed by two light sources separated 60° in azimuth and orientated so that an apex of the hexagonal contour points directly towards each light source. (After Williams and Smith, 1958.)

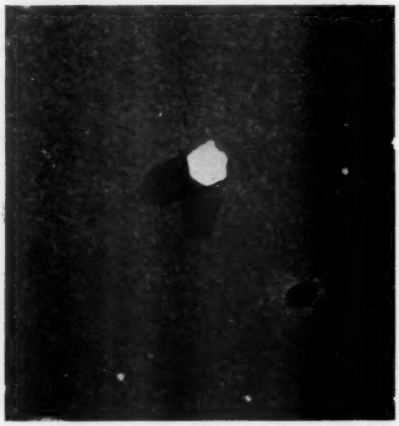


FIG. 7.—A frozen-dried, doubly-shadowed particle of TIV, orientated similarly to the icosahedral model shown in fig. 6 and exhibiting similar shadows. (x 54,000.) (After Williams and Smith, 1958.)

CHEMICAL COMPOSITION OF VIRUSES

Shortly after Stanley isolated the virus of tobacco mosaic in 1935, Bawden and Pirie and their co-workers (1936) showed that it was a nucleoprotein, and this holds good for all the viruses so far isolated and purified. As we have already pointed out, the nucleic acid in plant viruses is RNA and in animal viruses RNA or DNA, whilst in the bacterial viruses examined so far it is exclusively DNA. In the very small viruses there is no other constituent except protein and nucleic acid, although in some of the larger viruses from the higher animals, such as vaccinia, lipids are also present.

The tobacco mosaic virus consists almost entirely of protein and ribonucleic acid in the proportion 94.4:5.6. The general elementary composition is approximately C, 50 per cent.; H, 7 per cent.; N, 16.7 per cent.; S, 0.2 per cent.; and P, 0.54 per cent. Variation in these values is reflected in the minor amino-acid differences found in various strains. Each protein subunit in the TMV particle is a single peptide chain containing about 145

amino-acids. The carboxyl end of the chain is terminated by threonine, the sequence being proline, alanine and threonine.

New information bearing on the structure of TMV, and of its protein in particular, comes from the work of Harris and Knight (1955) who observed that the enzyme carboxypeptidase liberates one, and only one, amino-acid residue from TMV and that this amino-acid is threonine. Carboxypeptidase only attacks the carboxyl-terminal end of polypeptide chains, and the action of the enzyme is stopped in this case after the first link is broken. The second one happens quite by chance to be resistant, the proline link not being broken by the enzyme. The number of threonine molecules liberated indicates that there is one for every 17,000 in molecular weight. The bulk of the evidence therefore is that the tobacco mosaic virus has polypeptide chains of about 17 to 18 thousand in molecular weight, possibly in pairs, all of which have similar, if not identical, structures, and that they are arranged in some regular order to form a tubular molecule containing a core of nucleic acid and are composed of about 2,800 of such sub-units (Markham, 1959). This chemical evidence on the structure of TMV is amply confirmed by the results of x-ray analysis (see fig. 2).

MULTIPLICATION OF VIRUSES

It was shown by Markham and Smith (1949) that the purified virus of turnip yellow mosaic would separate, after centrifuging, into two portions called the 'top and bottom components'. On the electron microscope the two kinds of particles looked similar but the top component was of lower density and contained no nucleic acid. Moreover, infectivity was confined to the bottom component which did contain the nucleic acid. This was the first definite proof that the infectivity of a plant virus was centred in the nucleic acid of the virus particle and that the nucleic acid was inside the protein coat. Since then a number of other viruses has been shown to have top and bottom components and empty shells have been observed in several animal viruses as well.

A great step forward was made by Gierer and Schramm (1956) and Fraenkel-Conrat (1956) who showed independently that the RNA of TMV could initiate infection in the absence of the protein part of the virus particle. Furthermore, it has been shown by Fraenkel-Conrat and Williams (1955) that the protein and RNA can be separated and the two repolymerized, or the protein can be polymerized by itself. In the latter case some controlling factor seems to be lost and the resulting protein rods grow larger than the normal size of TMV particles (350 mμ × 15 mμ). When the protein and the RNA are polymerized the infectivity of the resulting rods is about 60 per cent. of the infectivity of normal TMV.

It has been observed on several occasions that after a virus enters a susceptible cell there ensues a period, called the 'eclipse phase', when no virus is detectable. This phenomenon has also been observed with TMV; furthermore, the eclipse phase is shorter when nucleic acid alone is inoculated

into the plant than when whole virus is used. This is what would be expected if during the eclipse phase the nucleic acid has to be denuded of its protein coat before replication can begin. It is possible that the protein merely protects the nucleic acid from the enzymes in the cell. We can therefore visualize a kind of sub-assembly system for making the TMV; the sub-units are made on the information contained in the RNA and then more and

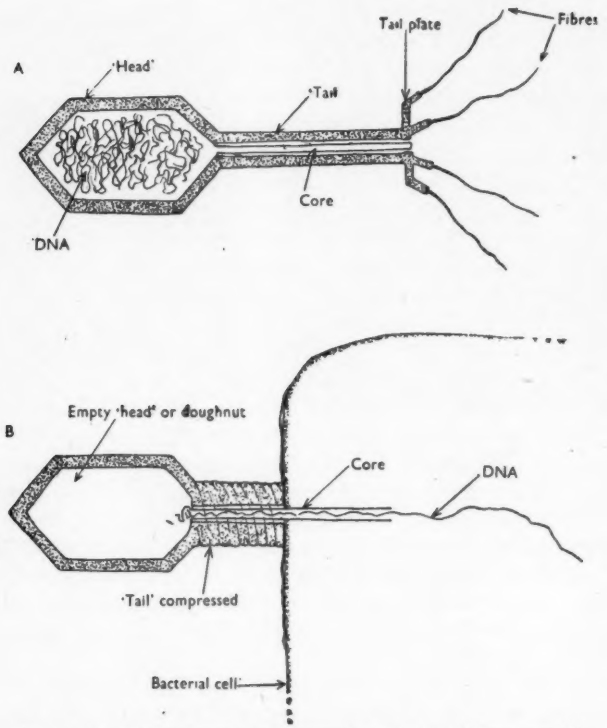


FIG. 8.—(A) Diagrammatic representation of a T_2 'phage particle showing the 6-sided 'head' containing the strands of DNA, the 'tail' with its central core, the 'tail' plate, and fibres. (B) The same 'phage particle attached to the bacterial cell; the 'tail' has contracted, the central core has penetrated the wall of the bacterium, and the DNA has passed down into the cell.

more sub-units are made. It is easier to replicate these small sub-units and then to build them up than to build up the virus particle with larger units. For the smaller viruses with icosahedral symmetry Klug calculates that 60 identical sub-units is the largest number which can be packed as a nearly spherical shell.

The most detailed picture of virus replication, however, has been obtained from the studies of the T_2 and T-even bacterial viruses or phages. It will

first be necessary to describe in some detail the structure of the virus particle because the structure is very much concerned in the beautiful mechanism of replication. The general shape of the phage particle is like that of a tadpole with a 'head' and a 'tail'. In the electron microscope both head and tail are easily distinguished but the tail has been found to be composed of an inner core and an outer cover. This can again be differentiated into a distal and a proximal part; the distal part seems to be composed of fibres which appear to be appendages to the tails (Kellenberger and Arber, 1955; Williams and Fraser, 1956). The tails end in a kind of tail plate to which these fibres are attached (fig. 8). It was first shown by Anderson (1953) how the phage particle infects the soil. Contrary to what might be expected the virus attaches itself tail first to the bacterial cell wall which is then penetrated and the DNA contents of the head pass down into the bacterium (Hershey and Chase, 1952).

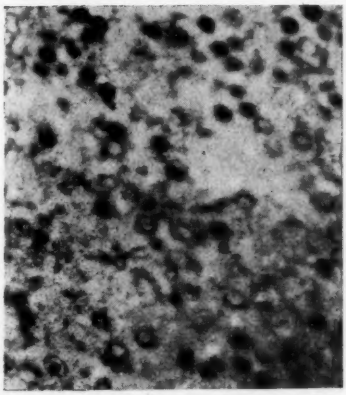


FIG. 9.—Ultra-thin section through the fatbody of a larva of *Tipula paludosa* infected with TIV; note the empty shells, half-filled and mature particles. (x 20,000.)

In an infection of *Escherichia coli* by T_2 phage, the breakdown of the bacterial nucleus is accompanied by the formation of marginal vacuoles containing DNA, from which the pool of phage DNA develops some minutes later. The phage DNA starts to increase six to seven minutes after infection. Then, about nine minutes after infection, the protein precursors, immature phages and, finally at thirteen minutes, complete phages appear in the infected cell (Kellenberger *et al.*, 1958).

An interesting phenomenon, the exact significance of which is not fully understood, has been observed with a number of viruses from both plants and animals. This is the occurrence of fully formed but empty virus membranes; they have been observed in the viruses of turnip yellow mosaic, of influenza, of poliomyelitis, of a frog kidney tumour and in the *Tipula* iridescent virus (TIV). They appear to differ from the empty heads of bacterial viruses since these are known to be left outside the bacterial cell after the injection of the DNA. In the case of TIV it has been suggested (Smith, 1958) that these empty shells may represent a stage in the multiplication of the virus. They only occur in large numbers in the early stages of the disease but they show considerable variation in their contents. Some may be completely empty, others contain a few strands of material which might be DNA whilst others may contain a darkly staining central body, and so on up to the presumably mature virus particle. In figure 9

is an electron micrograph of an ultra-thin section of the fatbody from a larva of *Tipula paludosa* infected with TIV.

CONCLUSION

To wind up this short discussion on the nature of viruses it may be opportune to give a definition of the viruses. Many such have been attempted but the one which seems appropriate here is that suggested by Lwoff (1957): 'Viruses are infectious, potentially pathogenic nucleoprotein entities, with only one type of nucleic acid, which reproduce from their genetic material, are unable to grow and divide, and are devoid of enzymes'.

I am indebted to Miss Margaret Short for drawing the diagram of the bacteriophage and to my colleague, Dr. Roy Markham, F.R.S., for some suggestions. Mr. G. J. Hills took the electron micrograph for fig. 1.

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RESPIRATORY VIRUSES, INCLUDING THE ADENOVIRUSES

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ACUTE viral infections of the respiratory tract are among the most important organic illnesses in Britain. They cause serious losses of time and efficiency at school and at work. They may also precipitate dangerous relapses in persons suffering from heart disease and chronic bronchitis. The influenza viruses have been known and studied in the laboratory for some years. They cause well-defined epidemics and some endemic disease. During the last five years many other viruses have been isolated from cases of respiratory illness. These 'newer' viruses are the subject of this article, but this field of research is expanding rapidly at the moment, and it will be impossible to review completely some subjects such as the adenoviruses.

THE TECHNIQUES OF VIRUS ISOLATION

The main reason for the spate of discovery of viruses is the application of tissue-culture techniques. Viruses can only multiply in living cells. The range of species and types of cell in which they will multiply may be very limited. The cultivation of poliomyelitis and related viruses in tissue cultures of human and monkey cells is a well-known example of how these new techniques have surpassed and for many purposes rendered obsolete the methods of animal inoculation.

The cultures used in the study of respiratory viruses have been, first, human epithelial cells, usually obtained from malignant tissue, and adapted to grow rapidly and continuously in tissue culture; they are often called transformed cell lines and the HeLa cell is a well-known example. Secondly, great use has been made of cultures of cells of monkey kidney dispersed by trypsin and capable of growing in culture for a few weeks. Each type of culture has some practical disadvantages but, as will be seen later, more than one type of cell must be used as there are viruses which will grow in one type of cell and not in others. The range of artificial hosts can be further extended by using a variety of media: serum-free media, including synthetic media such as Parker's 199, have been especially useful.

The viruses have in most cases been recognized because virus-infected cells degenerate and this degeneration, or cytopathic effect, can be readily recognized by inspecting the culture under the low power of the microscope (fig. 1, 2). It is clear, however, that some viruses infect culture cells without causing obvious degeneration. Recently it was shown that red cells added to the culture medium will stick to culture cells infected with influenza virus and other viruses. This test is called hæmadsorption (fig. 3).

RELATIONSHIP BETWEEN VIRUS INFECTION AND ILLNESS

It is well known that virus infections may occur without evident illness. Minor respiratory infections are common and a virus cannot be recovered by present techniques from the throat of patients with most of such illnesses. Therefore if a virus is recovered from such a case it is always possible that it is a coincidence, and that the virus infection has nothing to do with the

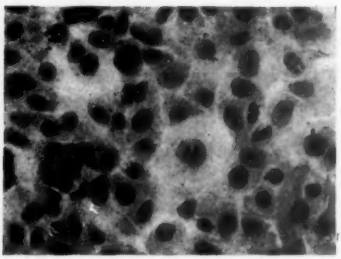

FIG. 1.—Tissue culture of uninfected HeLa cells (x 135).

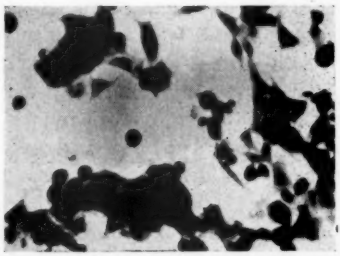

FIG. 2.—Tissue culture of cells infected with adenovirus type 5. Note clumps of rounded cells (x 135).

illness. To establish the relationship of the virus to the disease it is desirable, first, to show a rise in specific antiviral serum antibody during the course of the illness and, secondly, to show that persons from the same community who have no respiratory illness are not excreting virus and do not show antibody rises when tested in the same way and at the same time as the patients. It is valuable additional evidence if a virus occurs in association with some specific disease pattern on different occasions and in different areas. If a specific virus vaccine prevents clinical illness then this is very strong evidence that the virus causes disease. Because such studies take time and some of the viruses have been isolated only recently, evidence of this sort is not available in all cases. Sometimes the virus has been inoculated into human volunteers living in isolation. Such experiments, if not carefully conducted, may be misleading, but they can give proof that the virus multiplies in man and indicate the sort of disease which the virus might cause under field conditions.

THE ADENOVIRUSES

The first viruses of this family were discovered by culturing tonsils and adenoids removed at operation. Cells grew out at first and were then destroyed by the virus lying latent in the tissue (Rowe *et al.*, 1953). It was found that there were many serotypes of these adenoviruses, and the total number of types now stands at eighteen (Rowe *et al.*, 1958). Hilleman and Werner (1954) showed that a virus of this group (type 4) caused a disease of military recruits, namely A.R.D. (acute respiratory disease) which in this country is known as febrile catarrh (Stuart-Harris, 1953). This work has been confirmed by others, and serotypes 3, 7 and 14 have also been

found in this condition. Serotypes 3 and 7 also cause a specific infection of children called pharyngoconjunctival fever. Epidemic kerato-conjunctivitis, which affects mainly shipyard workers, is apparently due usually to type 8 (Jawetz, 1959), but other serotypes have been found in related conditions. Various serotypes of adenovirus have been isolated from the lungs in cases of fatal pneumonia in infants (Chany *et al.*, 1958).

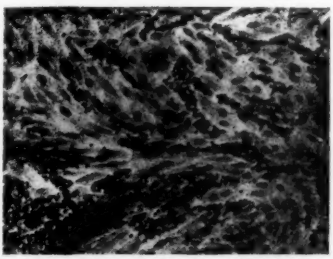

FIG. 3.—Hæmadsorption. Calf kidney cells infected with influenza A virus and treated with human red cells. Red cells have stuck to the infected culture cells. The same appearances are seen in cells infected with parainfluenza viruses (x 100).

The adenoviruses may cause up to 90 per cent. of the respiratory illness in recruit camps, but only 2 per cent. of adenovirus infections are found in serological surveys of cases of acute respiratory infections in civilians. Adenoviruses seem to have been found in every country in which they have been sought.

When given to volunteers adenoviruses cause febrile pharyngitis or conjunctivitis and pharyngitis; the clinical type seems to depend upon the method of administration. Killed virus vaccines have been prepared by inactivating virus obtained from tissue cultures. These are treated with formalin as in preparing poliovirus vaccine. Injection of such vaccines causes a rise in the serum antibody levels and reduces the frequency of infections with the corresponding adenoviruses. The use of these vaccines is of obvious value in recruit camps, but without further epidemiological research we cannot at present define what groups of civilians would benefit from them.

THE PARAINFLUENZA VIRUSES

These viruses are closely related to mumps virus and less closely to the influenza viruses. The first to be isolated was a strain of parainfluenza 1 which was recovered by inoculation of mice and eggs with material from Japanese children suffering from pneumonia (Kuroya *et al.*, 1953) and Russian children with 'croupous' pneumonia (Zhdanov *et al.*, 1957). It has also been found in an epidemic of a disease similar to influenza affecting adults in Vladivostok (Gorbunova, 1957). The virus has previously been called new-born pneumonitis virus, HVJ, Sendai virus and influenza D. There are antibodies in human sera collected in the United States (Jensen, Minuse and Ackermann, 1955) and Britain and rises occur occasionally during acute respiratory infections, but the virus has never been recovered in either country. It is possible that mumps virus (De Meio and Walker, 1957) or a slightly different strain of parainfluenza 1 virus is responsible for the antibodies. This strain of parainfluenza 1 virus can only be isolated in tissue cultures, and has been called HA 2 (hæmadsorption virus type 2)

by American workers (Chanock *et al.*, 1958) and also Cop 222 (Petersen and von Magnus, 1958). American workers have detected HA 2 virus infection in children with various acute feverish respiratory infections, especially croup, and rarely found it in children in a control group.

The parainfluenza type 2 virus is also called CA (croup associated) and ALTB (acute laryngo-tracheo-bronchitis) virus. This virus has been isolated in tissue cultures from American and Canadian children suffering from laryngo-tracheo-bronchitis (Chanock, 1956). Infected cultures develop striking vacuolated giant cells (fig. 4). Control subjects were not studied in these investigations but the virus has been found recently in the throats of London children suffering from croup.

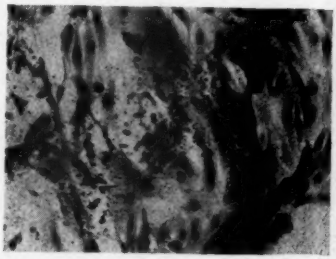

FIG. 4.—Monkey kidney cells infected with parainfluenza virus type 2. A focus of degeneration. Some cells have disintegrated and others have formed giant cells (x 100).

The parainfluenza type 3 virus, also called HA 1, was first isolated from American children suffering from acute respiratory tract infections ranging from mild cold-like illnesses to pneumonia (Chanock *et al.*, 1958). The virus was rarely found in children with other conditions. This virus has also been found in Britain (Sutton, Clarke and Tyrrell, 1959) in infants with the syndrome of coryzal bronchitis. It seems to be more prevalent than either parainfluenza 1 or 2. The American workers estimate that parainfluenza viruses 1 and 3 caused about 20 per cent. of the acute respiratory illnesses in the children they were studying (Chanock *et al.*, 1959). Both types of virus have been recovered from a small percentage of London children with acute respiratory infections but it is too early to make comparisons with the American survey.

When the parainfluenza viruses types 1 and 3 are administered to adult human volunteers the volunteers become infected and usually develop illnesses resembling the common cold, but occasionally a more severe febrile infection occurs. Virtually nothing is known of infections of adults by these viruses under natural conditions.

ECHO VIRUSES

The full name of these viruses (enteric cytopathogenic human orphan) arises from the fact that they were first found in the fæces of children without disease. They cause degeneration of cells in tissue culture and have no known 'parent' disease, but certain ECHO viruses have recently been recovered from children with respiratory disease.

A strain of ECHO 11 virus ('U' virus) was found in the throat and fæces of Swedish children with non-diphtheritic croup, and in others with minor respiratory infections; the virus could not be recovered from children

attending a hospital casualty department in the same town. The virus has been isolated elsewhere from children with no respiratory disease. In recent experiments human volunteers were inoculated intranasally with the Swedish strain and developed an illness with fever, mild abdominal discomfort, distension and some diarrhœa (Buckland *et al.*, 1959).

ECHO 20 virus was first recovered from young American children with

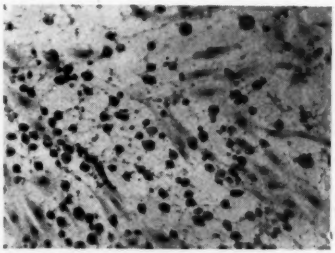

FIG. 5.—Degeneration of monkey kidney cells infected by ECHO virus type 11. This is like the degeneration produced by polioviruses and all other ECHO viruses except type 10 (x 100).

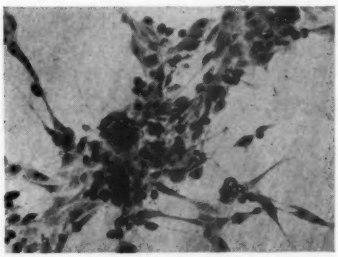

FIG. 6.—Degeneration of monkey kidney cells infected by ECHO virus type 10 (x 100).

febrile illness exhibiting respiratory symptoms including coryza and pharyngitis and also diarrhœa and other abnormalities of the fæces. There was no control group. In adult volunteers this virus produced fever, sore throat and sometimes coryza.

ECHO 10 virus has biological properties distinct from those of other ECHO viruses—for example it is larger and produces a quite different cytopathic effect (fig. 5, 6). One strain has been shown to produce an illness in chimpanzees like the common cold of man. Many strains have been isolated from children living in a residential nursery but the infected children seem to have little more respiratory symptoms than usual.

OTHER VIRUSES

Two closely related viruses, J.H. (Price, 1956) and 2060 (Pelon *et al.*, 1957), were isolated in the United States in 1953 and 1954 from young adults and children affected by an illness manifesting coryza, sore throat and fever. The viruses share many properties with the ECHO virus group. These viruses have not been isolated elsewhere, and control subjects were not tested, but a vaccine was prepared against the J.H. strain and apparently protected children against the infection and clinical illness (Price, 1957). Antibodies against the J.H. virus were found in sera collected in Britain (Tyrrell and Bynoe, 1958) but the virus has not been recovered. It has apparently disappeared from Baltimore where it was first found.

Another virus, called Coe, was isolated in California from Servicemen with mild acute upper respiratory tract infections. Its properties resemble

those of ECHO viruses but, unlike typical ECHO viruses, it grows in HeLa cells and not in monkey kidney cultures. Similar viruses have been recovered from Servicemen in England suffering from febrile upper respiratory tract infections.

Finally, an entirely unrelated virus has been shown to cause a disease like a common cold in chimpanzees (Morris *et al.*, 1956) and has also been

Respiratory illness	Associated viruses
Coryza with or without fever	Parainfluenza 3; J.H.; 2060; ECHO 20; Coe
Febrile pharyngitis, A.R.D.	Adenovirus 3, 4, 7, 14; Coe
Pharyngoconjunctival fever	Adenovirus 3 & 7
Non-diphtheritic croup Acute laryngo-tracheo-bronchitis	Parainfluenza 1 & 2; ECHO 11
Bronchopneumonia	Parainfluenza 3; Respiratory syncytial virus

TABLE I.—Some clinical types of respiratory illness and some associated viruses

isolated from children in Baltimore (Chanock *et al.*, 1957). It has been called respiratory syncytial virus, or CCA (chimpanzee coryza agent). Serological tests indicated that it had infected children suffering from a wide variety of respiratory infections. There were many cases of apparently symptomless infection. The Baltimore workers concluded that the difference between the frequency of infections in the children with and without respiratory symptoms was not significant, but it would not be surprising if further studies establish that this virus does occasionally cause disease.

THE COMMON COLD

It is still uncertain what proportion of respiratory illness is caused by the viruses already described, but it is probable that the illnesses they cause are usually febrile and predominantly of children. It is my opinion that the typical common cold, or acute afebrile infectious coryza, is usually caused by one or more families of viruses which cannot as yet be cultivated and studied in the laboratory. Even here, however, some progress has been made in recent years by the use of volunteers (Andrewes, 1959), and it has been shown that the virus can be neutralized by human gamma-globulin (Jackson *et al.*, 1958). Also, infection with a cold virus collected in one year will not protect against infection with a virus collected in another year, but it will protect, for at least a period of months, against reinfection with the same virus (Jackson and Dowling, 1959).

CONCLUSION

It is unwise to look too far into the future but it is probable that in the near future still more viruses pathogenic in man will be recovered from the

respiratory tract. It will probably be many years, however, before the relative importance of each has been discovered, or the full range of clinical illness in which each can play a part. Some features of the present position are summarized in table I. We may well find in the future that waves of apparently similar respiratory illnesses are caused by a procession of antigenically and biologically different viruses. When we know the important members of the procession it may be possible to use a vaccine or some other specific prophylactic to lighten the load of disease in the community.

I wish to thank Mr. M. Young for preparing the photographs.

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THE ENTEROVIRUSES

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THE family of enteroviruses now includes the poliomyelitis, Coxsackie and ECHO groups of viruses. Each group is composed of a number of immunologically distinct viruses.

TYPES OF VIRUS

There are 3 types of poliomyelitis virus, 25 known types of Coxsackie virus of which 19 belong to group A and 6 to group B, and 28 known types of ECHO virus. Newly identified types are still being added to the Coxsackie and ECHO virus groups.

Poliomyelitis has been a known virus disease for many years but it was not until 1949 that the existence of three separate virus types capable of causing the disease was finally recognized. These were subsequently designated as types 1, 2 and 3 from the frequency with which they were found in the first hundred strains typed (Committee, 1951). The discovery of the Coxsackie and ECHO groups was closely linked with poliomyelitis investigations. During a search for experimental animals susceptible to poliomyelitis viruses, Dalldorf and Sickles (1948) isolated from children with paralysis viruses which were not poliomyelitis, but which caused paralysis and death of new-born mice. They named the new viruses after the town of Coxsackie in New York State in which they were found. Strains of poliomyelitis virus were also isolated later from the affected children so that the role of Coxsackie viruses in causing paralysis was, and still is, not clear. Coxsackie viruses have since been found in association with other clinical syndromes and have also been isolated from healthy persons. The differentiation into groups A and B has been based upon the pathological changes found in the paralysed mice. In group A extensive destruction of voluntary musculature occurs with no other lesions, and in group B there are focal lesions in the embryonic fat pads, brain, heart, pancreas and voluntary muscles.

Tissue culture methods for virus isolation in which virus multiplication is indicated by cell destruction, the so-called cytopathic effect, led to the finding of viruses other than poliomyelitis in fæcal suspensions (Robbins *et al.*, 1951). Most of these differ from Coxsackie viruses in that they do not affect new-born mice. In further studies these viruses have been isolated from persons suffering from a number of clinical syndromes. They became known at one stage as orphan viruses because they could not be identified as the etiological agents of distinct diseases. They have also been isolated from healthy children and when obtained from this source were termed human enteric viruses. As a compromise they have now been called enteric cytopathogenic human orphan or ECHO viruses (Committee, 1955). Finally

the three groups have been brought together as enteroviruses (Committee, 1957).

VIRUS CHARACTERISTICS

The enteroviruses under discussion are those with a human host cycle, but it should be remembered that animals, including cattle, dogs, monkeys and pigs, all harbour distinct types of enterovirus. Transfer between animal species, although it can occur, is limited. Of the human enteroviruses, poliomyelitis may be transmitted to chimpanzees and to some species of monkey by parenteral inoculation and to a lesser extent by feeding. Man is considered to be more susceptible than these animals to alimentary tract infection with poliomyelitis viruses but less liable to their neurotropic effects. Small rodents such as mice, cotton rats and hamsters have a limited susceptibility, in particular to type 2 virus after intracerebral or, more often, direct intraspinal inoculation. This susceptibility may be enhanced by previous treatment with cortisone. The isolation of poliomyelitis virus from a budgerigar has been reported (Sommerville *et al.*, 1958), but other studies have confirmed that this is a rare event. Most strains of poliomyelitis virus are now isolated in tissue culture. A wide range of primary culture cells, including monkey and human kidney, human amnion and human embryonic tissue, has been found susceptible as have continuously cultured cells, of which the most widely used are HeLa cells originally derived from a primary carcinoma of the cervix.

The Coxsackie viruses have been isolated most frequently in new-born mice. These mice remain fully susceptible to the rapidly multiplying group A viruses up to three or four days of age, but gradually become more resistant after this time. The group B viruses grow more slowly, and maximum susceptibility is found in mice less than twenty-four hours old. Adult mice are for the most part resistant although group A types 1, 7 and 14 may retain an ability to attack the anterior horn cells of the spinal cord and some group B strains may cause pancreatic degeneration after intraperitoneal inoculation. This degeneration leads to wasting and death of the mice. Only a small number of group A viruses but almost all the group B viruses will grow in tissue culture cells used in most laboratories so that the latter have more often been found in association with human disease.

A feature of the ECHO viruses is that they may be readily isolated from fæces in primary cell cultures such as monkey kidney or human amnion but can be adapted to cells such as HeLa cells only with difficulty after a number of passages. Recently a number of the strains of ECHO type 9 virus which were responsible for many outbreaks of fever and aseptic meningitis has been found, after tissue culture passage, to cause Coxsackie group A lesions in new-born mice. The classification of these strains is at present subject to argument.

Other characteristics have been defined only to a limited extent but,

despite the large number of immunological types, the Coxsackie and ECHO viruses seem for the most part to resemble the poliomyelitis viruses in being very small in size, resistant to the action of ether, and able to survive for considerable periods in the absence of living susceptible cells at temperatures up to 18° to 20° C. At higher temperatures inactivation occurs more rapidly. This ability to survive may be of importance in promoting or maintaining the spread of infections.

Conforming to the pattern established with the poliomyelitis viruses, human enterovirus infections are considered to result from the ingestion of virus by mouth. The experimental feeding of poliomyelitis viruses to monkeys or chimpanzees has been followed by all grades of the disease from inapparent infection to severe paralysis. This is in agreement with human experience of poliomyelitis. Investigations in experimental animals and also in man have shown that virus passes from the pharynx to the lower alimentary tract where multiplication takes place, followed by excretion of virus in the fæces. Some virus multiplication may occur in the pharynx at this early stage of infection but when the amount ingested is small virus quickly disappears from this site. Later, at the end of the incubation period and during the first few days of clinical illness, virus often reappears in the pharynx. As well as being excreted in the fæces virus passes to sites within the body including the reticulo-endothelial tissues. This leads to antibody formation but before its appearance there may be a viræmia which allows the virus access to tissues such as brain, spinal cord, pharynx, meninges or myocardium. Having gained a foothold in one or other of these tissues the virus can multiply in susceptible cells, such as the anterior horn cells of the spinal cord, and destroy these. When a cell is destroyed virus is released and is able to invade contiguous cells. The focus of infection may expand until it becomes sufficiently large to produce a clinical effect such as paralysis, or it may become localized due to the protective effect of antibody which by this time has begun to appear in the circulation. Apart from poliomyelitis, which has the disadvantage that the brain and spinal cord are less accessible to the action of circulating antibody, most enterovirus infections tend to be self-limiting except perhaps those occurring in the very young whose antibody mechanisms are less well developed.

EPIDEMIOLOGY

Like other alimentary tract diseases enterovirus infections become more prevalent during the summer and autumn although localized outbreaks may occur at any time during the year. In describing an outbreak of aseptic meningitis with exanthema caused by an ECHO type 9 virus, Galpine and his colleagues (1958) noted the occurrence of widespread Sonne dysentery in the same area at the same time. Specific reasons for the increased number of infections are obscure and, although communal mixing and feeding may

play some part, the gathering together of large crowds for short periods does not by itself seem of importance. Close and intimate association is necessary for the spread of infection. Bradley and Richmond (1953) found little correlation between the incidence of poliomyelitis and the degree of temperature and humidity, although it appeared that only when the temperature had risen above a certain point was an increased incidence likely to be found.

In contrast to their presence in the throat, which occurs only during the first few days after the onset of illness, enteroviruses are excreted in the fæces in considerable amounts and for relatively long periods. Children are the most susceptible members in families and are also the most persistent excretors of virus. Once the virus has gained access, every susceptible member of a family tends to be infected, although not all necessarily develop a clinical illness. Outside the family, contact between children such as occurs at school is effective in spreading viruses. As well as the ordinary possibilities of transfer from hand to hand or hand to mouth there may be additional hazards from the use of communal lavatories (Darlow and Bale, 1959). Before resorting to measures such as closing the schools or imposing quarantine restrictions in the face of an outbreak of illness it is as well to reflect that before the decision is made the viruses have probably already circulated widely. Even with poliomyelitis most of the infections are subclinical, although a natural immunity does develop.

In studies of poliomyelitis it has been shown that the viruses are excreted by about 90 per cent. of paralytic patients, particularly children, during the first seven to ten days of illness. The proportion of patients continuing to excrete virus gradually diminishes thereafter but may still amount to 10 per cent. after ten to twelve weeks. In addition, healthy contacts of cases have been found to excrete as much virus, and for as long periods, as the patients themselves. Poliomyelitis and Coxsackie viruses have been readily isolated from urban sewage during the summer and autumn even when there have been few or no instances of disease. The indirect spread of infection due to enteroviruses is limited in communities with modern systems of sanitation as compared with communities in which methods of sewage disposal are primitive or non-existent.

Studies of other enteroviruses have been less detailed. Although the picture is similar, in some instances at least, excretion of viruses is less prolonged. It should be remembered also that viruses such as adenoviruses and herpes simplex viruses, which usually affect the respiratory tract and mouth, have been found in the fæces.

Because of the ease with which enteroviruses have been isolated from the fæces of healthy persons, proof that these viruses are the causative agents in outbreaks of illness must depend upon their isolation from a much higher proportion of the cases than from healthy non-contacts living at the time in the same area. In the patients themselves virus isolation from materials

other than fæces is also helpful. Although rarely found in poliomyelitis both Coxsackie group B and ECHO viruses have been readily isolated from cerebrospinal fluid in outbreaks of aseptic meningitis. Enteroviruses have also been found in central nervous tissue and the myocardium in fatal illnesses. Some enteroviruses have been associated with outbreaks of respiratory infection occurring during the winter months. Despite this, reports of the presence of enteroviruses in the saliva or in the nose have been rare.

Not all the enteroviruses have yet been associated with human disease, although the number keeps increasing. No chronic carriers have been found, so that it is considered that these viruses are not normal inhabitants of the alimentary tract. In addition, circulating antibodies appear in the course of infection. This important protective mechanism acts by interfering with the spread of virus, particularly during the viræmic phase. It forms the basis for the use of the present poliomyelitis vaccine in that, although natural infection of the alimentary tract is not prevented, the presence of circulating antibody should inhibit the later spread to the central nervous system.

The living avirulent poliomyelitis vaccines now being tried in different parts of the world act by infecting the alimentary tract and rendering it much less susceptible to a later natural infection; in addition they stimulate antibody production. These vaccines have the disadvantage that the viruses are excreted in the fæces for a variable period, with the consequent possibility of spread to non-vaccinated persons. If the viruses remain unaltered, this incidental effect can be beneficial. There is a slight chance, however, of their reversion to a form capable of inducing paralysis in man although this has not so far been shown to occur. The difficulty is that laboratory tests are not yet capable of clearly distinguishing such altered vaccine strains of virus from those likely to be circulating naturally. Suspicion of a vaccine might stultify a vaccination programme.

INFECTIONS ASSOCIATED WITH POLIOMYELITIS VIRUSES

The most common event after the ingestion of these viruses is an inapparent infection. This is known from the number of persons observed to have circulating antibody against one or more virus types by the time they reach adult life, although no history of illness suggestive of poliomyelitis can be given, and from comparisons of the number of persons who excrete viruses or develop poliomyelitis antibodies in the course of an outbreak of the disease in an area, with the number of clinical cases.

A recent investigation of the incidence of poliomyelitis viruses in normal children under five years of age in England and Wales showed that between 15 and 50 children were excreting virus for every notified case (Report, 1958). The investigation was limited in the ages of the children examined and in the technique used for virus isolation, so that the real number of excretors was probably higher.

Most persons who develop clinical poliomyelitis have a minor illness only, the disease being unrecognized in many instances. It is during this minor

illness that the viræmia occurs which may lead to involvement of the central nervous system and the development of spinal or bulbar paralysis, encephalitis, or aseptic meningitis in a small proportion of cases. The reasons why in a small proportion of patients a mainly benign infection should end in paralysis are obscure. It may be due partly to the virulence of the infecting organism, although it is not common to get more than one paralytic case in a family even when all its susceptible members have been infected and are excreting virus. It is widely held that paralysis may follow increased physical activity during the stage of minor illness (Russell, 1947), although Sutherland (1956), who re-examined this question, was unable to substantiate it in his series of cases.

Poliomyelitis appears to be on the increase throughout the world. For some time it has been an affliction of countries with a high standard of living, the more primitive communities being less affected. It has changed from a disease mainly affecting infants and young children to one affecting all ages and often has serious consequences in older persons who are deficient in immunity. There are the further hazards of the increased susceptibility, particularly to bulbar poliomyelitis, after tonsillectomy, and of provocation poliomyelitis after prophylactic inoculations intended to prevent other diseases. The use of the inactivated poliomyelitis vaccine has offset this to some extent as it is considered to afford 60 to 80 per cent. protection against the development of paralysis. Vaccine studies, however, have repeatedly shown that the type 1 virus component is less successful in inducing immunity than are the types 2 and 3 virus components. Type 1 virus is most often associated with clinical poliomyelitis and, because of this, paralysis may develop in previously immunized persons.

Recently, in underdeveloped countries where it has previously been rarely reported, there has been a number of outbreaks of poliomyelitis, mainly infantile in distribution. These have been correlated with a rising standard of living and a fall in the infant mortality rate.

INFECTIONS ASSOCIATED WITH GROUP A COXSACKIE VIRUSES

Despite the large number of types of group A virus in existence, evidence of their role in causing human disease is limited. In a number of poliomyelitis outbreaks, dual infection with poliomyelitis and group A viruses has been reported and the suggestion made that the presence of the latter viruses may in some instances account for unusually severe forms of illness. Experimental evidence in support of this hypothesis has been produced in that monkeys after combined inoculation with an attenuated type 1 poliomyelitis virus and a group A type 14 Coxsackie virus developed severe paralysis although neither strain of virus when given separately had this effect (Dalldorf and Weigand, 1958). Viruses isolated from patients with paralysis in Russia and found to differ from the standard types of polio-

myelitis virus were tentatively labelled type 4 poliomyelitis virus. Subsequent studies in Sweden and the United States identified these as group A type 7 Coxsackie viruses and confirmed by monkey inoculation their ability to cause paralysis.

Some group A viruses, including type 7, have been responsible for outbreaks of aseptic meningitis, a syndrome in which the same clinical picture may be caused by many agents including other enteroviruses. An exact diagnosis can only be reached by laboratory investigation during the course of illness.

Herpangina, described as a short specific febrile illness of childhood in which minute vesicles or punched out ulcers are found in the posterior parts of the mouth, has recently been shown to result from infection by a number of group A viruses (Huebner *et al.*, 1952). Another minor illness affecting children and adults with fever, inflammation of the mouth and throat with small vesicles and ulcers, and a maculo-papular skin rash mainly on the limbs with some vesiculation on the fingers and toes was reported to have been caused by a virus closely related to group A type 16 Coxsackie virus (Robinson *et al.*, 1958).

INFECTIONS ASSOCIATED WITH GROUP B COXSACKIE VIRUSES

All types of group B virus have been associated with outbreaks of aseptic meningitis or mild meningo-encephalitis. In many instances the causative virus has been isolated from the patient's cerebrospinal fluid. These viruses have also been responsible for many outbreaks of epidemic myalgia or Bornholm disease, both children and adults being affected. Characteristically, in some of the outbreaks children have developed aseptic meningitis and adults pleurodynia or other forms of myalgia, although the same type of virus has been responsible. Unlike the group A viruses dual infections with poliomyelitis viruses are uncommon. Experimentally, both in tissue culture and in mice, interference by group B viruses with multiplication of type 2 poliomyelitis virus has been demonstrated and there is some evidence that group B virus infections occur only at times and in areas where the incidence of poliomyelitis is low.

In recent years there have been reports from a number of countries of severe, often fatal, illnesses in new-born children with acute encephalitis and myocarditis; group B viruses have been isolated from these children. The illnesses have occurred at times when Bornholm disease has been prevalent in the community, with often a history of the mother being ill at, or shortly before, delivery. The babies have been infected either *in utero* or shortly after birth and the illnesses resemble those which occur in new-born mice when inoculated with group B viruses. Suggestions that group B viruses may cause myocarditis in older children and benign pericarditis in adults are less well substantiated and need further investigation.

INFECTIONS ASSOCIATED WITH ECHO VIRUSES

Although aseptic meningitis has been the illness most often ascribed to the ECHO viruses, not all the known virus types will cause it. In some outbreaks the meningitis has accounted for only a part of the total number of persons affected, with most having a non-specific febrile illness. Children are often affected and a characteristic feature has been the high infection rate in families. Sometimes a maculo-papular rash has developed during the illness, mainly on the face but spreading to the neck, shoulders and arms. Again, only a proportion of those ill have developed this. In this country viruses of different types have been isolated from patients with meningitis but the only widespread outbreaks reported have been caused by type 9 viruses. These outbreaks were widespread during 1955-56 but since then have not recurred and the type 9 virus has only rarely been isolated.

Investigation of unexplained outbreaks of diarrhœa has sometimes yielded ECHO viruses of different types, particularly in the summer and autumn. In a number of studies it has been shown that, although the frequency of excretion of poliomyelitis and Coxsackie viruses was similar in children with or without diarrhœa, a higher proportion of those with diarrhœa were excreting ECHO viruses of different types. Sometimes the ECHO viruses were associated with pathogenic types of bacteria. It was concluded that diarrhœa was a consequence of transitory infections with a variety of ECHO viruses, pathogenic bacteria or combinations of both.

A few types of ECHO virus have been isolated from outbreaks of mild respiratory illness, particularly in children. The significance of these findings is still being investigated.

DIAGNOSIS OF ENTEROVIRUS INFECTIONS

This entails the isolation of the causative virus and the demonstration of an increase in the amount of antibody against this virus during the course of the illness. The number of different virus types makes isolation essential, particularly when serological studies are contemplated, because there are no readily available group antigens such as those found with influenza viruses. Materials for virus isolation—fæces, throat swabs or cerebrospinal fluid—should be collected at the onset of illness and stored in a refrigerator, preferably frozen, until transferred to a virus laboratory. Virus isolation and identification usually take several days. Identification also depends upon the availability of diagnostic typing antisera.

For serological tests two samples of serum are necessary: the first taken early in the illness and the second during convalescence. The former sample provides the base line, as a high antibody content in a serum obtained late in the course of an illness is not significant if it is unchanged when compared with the earlier serum.

SUMMARY

The various types of enterovirus have been described, including a brief

history of their discovery, their characteristics in experimental animals and in tissue culture, and their behaviour in the human host.

The spread of these viruses in the community, the infections to which they may give rise and the steps necessary for diagnosis have been mentioned.

The importance of the enteroviruses lies in their potentiality for causing outbreaks of illness, particularly with neurotropic manifestations. In some countries this may be due to changing circumstances as a result of rising standards of living. In other countries the protection against some of these viruses provided by vaccination may bring to light new pathogens.

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PSITTACOSIS AND ORNITHOSIS

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Classical psittacosis in man takes the form of a severe febrile illness with toxæmia, many patients being delirious with the development of the typhoid state. At first there are few localizing symptoms or signs but, as the disease develops, it becomes clear that the lungs are involved. The lung lesions are proliferative in character and spread to involve all the lobes, but the changes are not such as to give the clear physical signs normally associated with pneumonia of bacterial origin. The syndrome is that of a severe atypical pneumonia or pneumonitis. A severe attack has clinically many resemblances to severe epidemic influenza, but it can also occur in a comparatively mild form.

EPIDEMIOLOGY

The diagnosis of an isolated case cannot normally be made either easily or speedily. Most isolated cases are diagnosed following an x-ray examination which shows a pneumonitis, and after complete serological examinations for antibodies against viruses known to be associated with pneumonitis but, as these antibodies are not present early in the disease, the diagnosis can be made only after the patient has been ill for some time. If there is a striking association between the patient and birds, and especially birds of the parrot family, the diagnosis might be tentatively made early on clinical grounds. Similarly, if the patient is one of many in an outbreak the diagnosis might be suspected from the outset, but outbreaks, though attracting much attention when they do occur, are very rare; there have been none of any considerable size in Britain.

Psittacosis is also a disease of birds, especially parrots, and when the disease was first described in man the association with parrots was clear—hence the name. In the early outbreaks described before the end of last century it often happened that an outbreak of disease among parrots preceded the human cases, but it has since become clear that birds remain infectious for long periods after recovery from an illness. Before the end of last century therefore it had been established that a disease of parrots could be communicated to man, and at that time Nocard isolated an organism which was thought to be of etiological significance. In 1930, there were outbreaks of psittacosis in many parts of the world, all associated with imported parrots. The disease was the subject of investigation in many countries, and it was established in Britain, America and Germany that the cause of the disease in parrots and in man was a virus (Bedson, Western and Simpson, 1930; Levinthal, 1930; Krumwiede, McGrath and Oldenbusch, 1930). Nocard's bacillus had already been shown to be *Salm.*

typhimurium which, though a pathogen, is not the cause of psittacosis.

Although the early cases of human disease had been contracted from parrots it became clear that the infection could be carried by all birds of the parrot family: e.g. budgerigars. About 1940, some ten years after the virus had been described and accepted as the cause of the disease, it was established that other birds were infected by the virus, or a similar virus, and could pass the infection to man. A considerable outbreak of the disease occurred in the Faroe Islands among those who prepared fulmar petrels for food, especially affecting the women who removed feathers, cleaned and salted the birds. Similar outbreaks, though none quite so extensive, have occurred in several large poultry stations in the United States, and again the people affected were those who prepared the birds for the market. In some of the outbreaks in the United States it was apparent that the infection within the station had been limited to one day, suggesting that the infection had been carried by birds from one farm. The American outbreaks were particularly associated with turkeys and ducks. These outbreaks associated with petrels, turkeys and ducks were outbreaks of serious disease.

Since 1940, when it was accepted that birds other than psittacines could carry the infection, a search has been made to identify the infection in other birds. A large number of bird species has been incriminated, and probably the most notable finding in this connexion is the heavy infection rate among wild pigeons, in which figures of 25 per cent. positive have been recorded. The incidence of the infection among birds appears to depend, to some extent, upon their habits: those that nest together in flocks being the species that are more likely to suffer. In the earlier outbreaks in which parrots had played so prominent a part, it often happened that there had been an outbreak of disease among them during the voyage when they were crowded under poor conditions. When it was established that birds other than psittacines could carry the virus it was suggested that the word ornithosis might be used and that the term psittacosis be reserved for the disease contracted from psittacine birds. There would appear to be little advantage in this, however, as the two conditions in man are essentially the same.

PSITTACOSIS GROUP OF VIRUSES

Many mammals and birds suffer from disease caused by viruses of this group and several different syndromes result. In birds, psittacosis or ornithosis takes the form of a generalized infection with special involvement of the liver and spleen. In man it is the lungs that show special involvement. There still remain, however, an encephalomyelitis of bovines, enzootic abortion of ewes and lymphogranuloma venereum, a venereal disease, of man. There is little doubt that there is a number of related viruses in the group and it would probably be best to regard the group as a genus in the biological sense. It requires extensive tests of antigenic structure and virulence to distinguish between the members, but it is probably justifiable to speak of the strains from epidemic abortion of ewes, feline pneumonitis

and lymphogranuloma venereum as separate species. It is doubtful, however, whether the demonstrable differences between strains from psittacines and strains from other birds justify the definition of separate species in the biological sense.

The virus is excreted in the fæces of birds long after they have recovered from any clinical illness. Infection is thought to spread among birds by dust from the droppings, and it is for this reason that the infection is more common in birds which nest in flocks. Man, too, is thought to acquire the infection by inhaling the dust of birds' droppings, but some parrot and budgerigar fanciers have been infected by allowing the bird to accept food from their lips.

The virus itself is of considerable interest to virologists. It is larger than most—200 mμ to 300 mμ—and can be seen intracellularly in stained smears of spleen of mice which have been experimentally infected. When these elementary bodies gain access to a susceptible tissue they undergo an interesting growth cycle during which large plaques appear before giving rise to an increased number of elementary bodies. This growth cycle has been extensively studied by biologists interested in the replication of viruses. The psittacosis virus is very pleomorphic and the intracellular matrix which makes up the inclusion body might mask the simple fact that the virus is multiplying by binary fission. Other investigators have suspected that there is a genuine cycle of development, probably with recombination of sub-units, as is thought to be the case with many of the smaller viruses. Because of the large size of the psittacosis virus there has been a suggestion that it does not properly belong with the other viruses and might be better classified with the Rickettsiæ.

CONTROL OF PSITTACOSIS

After the outbreaks in 1930, Britain and many other countries passed laws controlling the importation of psittacine birds. After it had been established that the virus was widely distributed throughout the bird kingdom, the ban was revoked in 1951, but reimposed in 1953 when it became clear that imported parrots had again been responsible for the occurrence of serious disease in man. It might be argued that, because of the high incidence of infection in sea birds and pigeons, any order to prohibit the importation of psittacines would play a small part in the epidemiology of the disease. The fact remains, however, that having regard to the population of psittacines in this country they are peculiarly liable to be associated with disease in man. Hence they are the subject of special legislation.

The virus rarely spreads from a sick patient to a healthy person. On the other hand it is notorious how often the virus has infected virologists who have handled it.

INCIDENCE AND LABORATORY DIAGNOSIS

Incidence.—Most cases recognized in this country are identified as the result of investigations made into cases of severe atypical pneumonia. Usually

this means a serological diagnosis based on the examination of blood taken early in the disease and in convalescence for antibodies to the psittacosis-L.G.V. group of viruses. About fifty cases a year are diagnosed by the Public Health Laboratory Service. Not all the cases giving serological evidence of infection by the viruses give a history of close association with birds, but a number of the more severe cases do. The suspicion has arisen that a variety or strain of virus might be peculiarly associated with human pneumonitis, and that the most exhaustive investigations would fail to reveal any association with birds. Pneumonitis is a common disease, and comparatively few cases are fully investigated for evidence of virus infection. This has led to the suspicion that many mild cases of 'psittacosis' would be identified if all patients with pneumonitis were submitted to extensive laboratory investigations. There is therefore a belief that many mild cases of psittacosis occur in this country. It happens in the history of many infectious diseases that once the disease is recognized in its severe form, milder forms are identified. It is not so many years since bacillary dysentery, as it occurred in this country, was attended by an appreciable death rate—according to hospital statistics. The same could be said of paratyphoid fever and salmonella food-poisoning.

Serological surveys have been made in different countries to gain some evidence upon the extent of infection by the psittacosis-L.G.V. group of viruses. In our own laboratory, in such a survey a comparatively low figure was obtained, just over 1 per cent. of samples having complement-fixing antibodies at a titre of 1:16 or over.

Laboratory diagnosis.—If the disease is suspected in the early stages the virus can be isolated from the sputum by injection into mice. To protect the mice from bacteria normally present in sputum some antibiotics are added to the injected material. The virus may also be isolated by culture in embryonated eggs. Very few cases are, in fact, diagnosed in this way. Most cases are diagnosed serologically: i.e. antibodies are shown to develop during the course of the illness. The antigen used is a dead suspension of classical psittacosis virus grown in embryonated eggs and made in such a way that only the heat-stable components are identified in the complement-fixation test. These components are shared by all members of the genus and thus the serological test gives evidence of infection by one or other of the members.

TREATMENT

All the modern antibiotics have been used in the treatment of psittacosis. None is strikingly successful but there is evidence that chlortetracycline and oxytetracycline are considerably better than the others.

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HERPES SIMPLEX AND VARICELLA-ZOSTER

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BECAUSE of a similarity in the type of cellular reaction in the infected tissues, i.e. multi-nucleated giant cell reaction and the presence of acidophilic intranuclear inclusion body at some stages in certain infected cells, there has been a suggestion that the virus of herpes simplex might be grouped with the virus of varicella-zoster in a system of classification (Scott, 1959). These viruses, however, are antigenically unrelated and their range of susceptible hosts is quite different. Herpes simplex affects a wide variety of experimental animals and varicella-zoster none. Confusion in the minds of some physicians from the use of the prefix 'herpes' with zoster has been encountered, and I prefer to consider herpes simplex and varicella-zoster separately rather than under the heading *herpes viruses*.

HERPES SIMPLEX

Herpes simplex is caused by a virus of which there appears to be only one antigenic type and no cross-relationship has been found with any other virus except B virus of monkeys. The disease has been recognized as a common complaint for many years and, because of its frequent recurrence in some patients in spite of all manner of treatments, has often provided a difficult problem in medical practice. It may occur in many forms, such as acute gingivo-stomatitis, rhinitis, keratoconjunctivitis and keratitis, meningo-encephalitis, infection of the genitalia, and occasionally as a disseminated systemic disease. Localized lesions may occur at the site of an injury (traumatic herpes) and their virus etiology not be suspected. An interesting example of focal lesions resembling a whitlow on the fingers of nurses has been described by Stern *et al.* (1959). Herpes simplex can appear at any age from birth onwards but the usual time of primary infection is between the second and fifteenth year. The general opinion is that once infection has occurred the virus persists in the body for the rest of the patient's life. Infection in the neonatal period is likely to occur only in infants whose mothers have not been infected so the infant has no passively transferred antibody. Passively acquired antibody will disappear and the infants will become susceptible about 4 to 6 months of age. If infection occurs in the first few months of life, particularly in infants with eczema, it may be very severe and even fatal. Primary infection in the adult has been rarely recognized, probably because of the general impression that herpes infection is universal but also because of the idea that normal adult epithelium is im-

permeable to the virus. These conclusions are both open to doubt. Until some specific treatment becomes available, herpes infection of the newborn, though not common, is one of the most important aspects of the disease because of the high mortality rate.

HERPES SIMPLEX IN THE NEONATAL PERIOD

The possibility of generalized infection in the neonatal period was first recorded by Hass, in 1936, as the result of a retrospective pathological examination of post-mortem material from a baby with necrotic lesions in the liver. The next cases were reported by Florman and Mindlin (1952) and Zuelzer and Stulberg (1952) who each carried out virus isolation studies in one case. We became interested in this problem in 1955 after carrying out virological investigations on a fatal case. Reports of 18 cases were found in the English literature and we were able to add four further cases which we had investigated in association with other colleagues as a result of their pathological investigations (MacCallum, 1956). Since January 1959 two further fatal cases have been investigated in Newcastle (Bird and Gardner, 1959; Wort and Gardner, 1959); another case was recently diagnosed histologically by France in London (1959). The serum of the mother of the latter baby did not contain herpes antibody. Further inquiry revealed that a herpetic pupil midwife had been on duty in the labour ward where the mother was present before delivery, and this girl developed herpetic lesions of the mouth a few days later (Elias-Jones, 1959). Although she was not the proven source of the baby's infection this is an excellent example of the potential danger.

The fact that five fatal cases were reported by Jack and Williams in Melbourne (1955) and three more in the past eighteen months (Jack, 1959), five fatal cases by Zuelzer and Stulberg and that we have records of seven fatal cases in England all suggests that this condition may not be rare in certain circumstances. Thus, although some pædiatricians who have been looking for such cases have not seen them in the past eight to ten years, this may be only an indication of the high rate of immunity of the mothers in their area. Some cases in the past may have been classed as bacteriæmias due to an unknown organism, because of the macroscopic yellow necrotic areas in the liver from which no bacterium could be isolated. The records of many of the reported cases are incomplete, and in others the investigations have been undertaken too late to determine whether primary infection of the mother had manifested itself at the time of delivery, and whether antibodies present were new or of long standing. In six cases, however, it is definitely stated that the mother was known to have had infection sometime preceding the end stages of pregnancy and one would have expected passive antibodies to be present in the baby's serum. If true, this suggests that these were inadequate, either qualitatively or quantitatively, to prevent entry of the virus and overwhelming multiplication at the site, leading to viræmia and fatal generalized infection, death being the result of encepha-

litis, or hæmorrhage into the lungs or adrenals as well as hepatic necrosis.

After consideration of these aspects of herpes infection we decided to investigate the state of immunity of the adult female population, which had not been done for many years except in some densely populated cities such as Manchester. It has been known for many years that in communities or households where people are closely associated and personal hygiene and habits are of a low standard it is likely that the infection rate with herpes virus is 90 to 100 per cent. In the family, one or other parent usually transfers the infection to the child and, depending upon his age and general health, the result may be anything from a symptomless infection, in about 90 per cent., to a stomatitis or generalized herpes or, rarely, an encephalitis or aseptic meningitis without a detectable superficial lesion. These facts have led to the general conclusion that herpes infection is present in most adults. In studies of adults, however, most of whom were females, in four different areas of England in 1956 this was found not to be true. The groups were not exactly comparable, consisting of patients attending venereal disease clinics and antenatal clinics, but most were from the latter. A significant level of neutralizing antibodies in a single serum was found in about 41, 55, 65 and 96 per cent. in the four different areas (MacCallum 1959a). The extremes were found in a crowded borough of London where 96 per cent. had antibody, and in a rural and semi-rural area where only 41 per cent. of 120 pregnant women had antibody. These different results are similar to those reported from Melbourne in 1939 between medical students on the one hand and patients attending hospital on the other (Burnet and Williams, 1939). Some workers have noted a similarity between the distribution of herpes and poliomyelitis antibodies in different types of communities but, if infection is present in one or other parent at the time of marriage, it is likely to spread to all members of the family, no matter what the social or economic level of the household may be. It is well recognized that from primary infection onward the presence of the virus may be manifest in a number of different ways. Some patients give no history at any time, some have recurrent attacks at the time of physiological upset such as menstruation, and others at the time of other stress. Because the most common site of persistence of the virus appears to be the buccal cavity, the most common site of the lesion is in this area at the time of upper or lower respiratory tract infection. In some patients the lesions always recur at the site of old fractures or burns or other scars.

SITE OF ENTRY OF THE HERPES SIMPLEX VIRUS

The site of entry of the virus is probably any exposed mucous membrane or superficial epithelium, so that entry could take place in the cornea or conjunctiva, nose, throat or skin. As viræmia has been proven by virus isolation it is evident that virus could reach the brain and meninges through the blood stream but possibly also through the olfactory nerve or some other pathway. It is notable that the temporal lobe of the cerebrum has been the

particular site of softening and inclusion bodies in patients with encephalitis shown to be due to herpes, but inclusions may be found more readily in other areas at the time of death if necrosis has been very extensive.

MECHANISM OF PERSISTENCE OF THE HERPES SIMPLEX VIRUS

The exact mechanism of the persistence of the virus in the presence of antibodies is not understood, but studies in the electron-microscope and by other techniques have shown that new virus particles are first seen in the nucleus of the cell (Scott *et al.*, 1953; Morgan *et al.*, 1954), and not in the cytoplasm or at the cell surface like the influenza viruses. It is possible that the essential particles for providing development of new virus may be transferred when the nucleus divides to form new cells. Alternatively, as suggested by studies in tissue cultures, the virus may pass from cell to cell through cell bridges or by breaking down of the cell membranes, thus avoiding contact with antibody present in intercellular spaces. Antibodies capable of protecting experimental animals, fertile hen eggs or tissue cultures appear within about seven days of onset of the primary infection, reach a maximum in twelve to twenty days (approximately) and remain at or about this level for the remainder of the patient's life. Injections of vaccine made from virus-containing tissues have naturally failed to stimulate any further antibody response or cause cessation of attacks.

One of the most interesting observations from an immunological viewpoint in recent years has been that children and adults with hypogammaglobulinæmia who are members of herpetic families, and almost certainly have been infected although no antibody is detectable, may not show any signs of infection, and if lesions are present they are no more severe than those commonly seen in normal individuals of the same age (MacCallum, 1959b). We have not had the opportunity, however, to observe a known exposure of such a child in the first three months of life when the disease is most severe. Another unusual type of herpetic lesion, possibly associated with the chronic infection, is keratitis, which Jones (1958) suggests may be due to the damage caused by continuing reaction between the persisting virus soaked up by the corneal stroma and local or circulating antibody.

PROPHYLAXIS OF HERPES SIMPLEX

Until comparatively recently it has been generally considered that herpes infection was just something one had to accept. One either had it or not, and most people became infected by late adolescence. There now seems to be good evidence that this is not so; all mothers do not possess antibody—in fact, as already mentioned, 59 per cent. of those attending an antenatal clinic in one area in England did not—and therefore the new-born infants of those who do not are susceptible to infection with this virus from midwife, nurse or visitor which can cause a severe and usually fatal illness. For this reason it is essential that the herpetic history of midwives, nurses and

attendants in maternity wards and nurseries should be known. It is preferable that those known to have had typical attacks should not work in such wards, and certainly they should be kept off duty if a herpetic lesion is seen.

Infants up to 3 months of age who are in known close contact with a case and whose mothers are not known to be herpetic, may benefit from gamma-globulin. Infants with eczema who are known contacts of herpes virus should receive 1000 mg. of gamma-globulin and this may be repeated if contact recurs after five to six weeks (Brain *et al.*, 1957).

Vaccines of dead or attenuated herpes virus have not been tested prophylactically in any large group of susceptibles.

TREATMENT OF HERPES SIMPLEX

There is no specific treatment. Attention should be given to prevention of secondary bacterial infection and to symptomatic relief. Vaccines of herpes virus have no effect on those already infected.

Herpes infections of the eye should be treated by an ophthalmologist. The body of opinion in the United States and some other countries condemns the use of cortisone for treating herpetic keratitis, but Jones (1958) believes that it may be valuable if used carefully in selected cases with minimal lesions.

VARICELLA-ZOSTER

In this section attention will be focused on some of the unusual features of chicken-pox and shingles and the results of recent laboratory investigations of the causative viruses. The relationship between these two conditions and their epidemiology should be clarified in the near future as a result of the use of tissue culture techniques developed for the study of these viruses by Weller and his colleagues (Weller, 1953; Weller and Stoddard, 1952). No attempt will be made to give a detailed description of the clinical features of these two diseases or the various types of treatment that have been tried without proven success. The replies to recent inquiries sent to colleagues in countries in different parts of the world indicate that the clinical picture of chicken-pox, its predilection for children, and the low resulting mortality remain unchanged in both temperate and tropical zones.

EARLY INVESTIGATIONS IN VARICELLA-ZOSTER

Fundamental information on many aspects of the pathology and clinical picture was obtained many years ago, particularly from the pathological studies by Head and Campbell (1900) of the lesions in the nervous system in zoster, and from the experimental inoculation into children and adults of vesicle fluid and crusts from patients with either varicella or zoster by Kundratitz (1925), Bruusgaard (1932) and others. In the laboratory, Netter and Urbain (1926), Paschen (1933), Brain (1933) and Amies (1933, 1934) showed that complement-fixing and agglutinating antigens were present in the vesicle fluid from patients with either varicella or zoster and each reacted to more or less the same degree with the convalescent serum of patients with either disease. All this work resulted in a firm background of

information on which the application of new virological techniques can proceed.

RELATIONSHIP BETWEEN VARICELLA AND ZOSTER

The main point of interest from the clinical viewpoint has been the relationship between varicella and zoster and the pathogenesis of the latter. The incubation period of varicella is twelve to sixteen days. The usual mode of spread is thought to be by direct contact and the period of greatest infectivity is probably before the appearance of the generalized rash. The nasopharynx is thought to be the site from which the virus is disseminated at this time. Vesicle fluid may be the source of infection but the usual failure to isolate virus from crusts in tissue culture indicates that the latter are of little or no danger. There is now a large number of reports of the occurrence of zoster, particularly in adults, after contact with patients with varicella, and also some examples of varicella after contact with zoster. In either instance, when determinable, the incubation period has usually been thought to be about fourteen days, but the fact that many zoster cases appear to arise spontaneously, i.e. without any known contact, or after irradiation or injury, makes it difficult to establish a definite incubation period. Stokes (1959) has recently stated his belief that zoster in adults usually appears three to seven days after exposure to varicella, and noted the similarity of the time interval to that of the accelerated response of a partially immune person to vaccinia. Second attacks of varicella are rare, but are not uncommon with zoster, suggesting that serum antibody prevents viræmia and epithelial involvement but cannot affect the virus in the cells of dorsal root ganglia, so that 'second attacks' of zoster are really relapses of a persistent latent infection as in herpes simplex.

Virus particles of similar size can be seen in, and isolated in, tissue culture from the vesicles of both diseases and a zoster virus has also been isolated from the cerebrospinal fluid of one patient (Gold and Robbins, 1958). What are probably specific virus inclusions have been found in numerous organs and the endothelial cells of blood vessels in fatal cases of varicella and in the dorsal root ganglia and other sensory ganglia and even in sensory nerve endings in zoster cases. Thus we know the sites of the final stages of the infection but we do not know the precise site of entry of the virus or the pathogenesis of either disease. Numerous investigators have suggested that the site of the lesions in the ganglia in zoster corresponds to the area at which virus entered: e.g. Cheatham (1953) described his findings in a fatal case from which he concluded that the virus entered the body via the sympathetic nerves of the œsophagus. Unfortunately there is no susceptible experimental animal in which the pathogenesis of the disease can be studied. When vesicle fluid from either zoster or varicella was inoculated intradermally into volunteers it usually produced only local lesions with occasional generalization of skin lesions ('varicella'), but susceptible child contacts of the inoculees developed varicella after either inoculation. As the

varicella virus is found in numerous organs and inclusions in blood-vessel walls it is natural to assume that viræmia has occurred (as in pox diseases or measles) following multiplication in some primary or secondary site. It is well recognized that second attacks of varicella are rare and it has been clearly demonstrated in tissue culture tests that neutralizing antibodies develop in convalescence. Thus there seems to be ample evidence that serum antibodies should play a part in immunity. Yet, in contrast to what happens in other diseases with viræmia, gamma-globulin does not appear to protect contacts, and it is generally stated that transplacental passage of immunity from mother to fœtus does not occur. It should now be possible with the aid of tissue culture techniques to throw some light on these unexpected findings.

VARICELLA-ZOSTER IN THE NEONATAL PERIOD

Varicella and zoster are both uncommon in the neonatal period but the case reported by Feldman (1952) deserves attention. The mother had varicella in childhood and zoster immediately before or at the beginning of pregnancy. The infant, the first of twins, was delivered by forceps with traction on one thigh. Four days later zoster-like lesions appeared on this thigh. Tests for zoster were not made, but tests for herpes simplex were negative. The other twin remained well but the obstetrician and the bacteriologist who collected the specimens from skin lesions developed zoster fourteen days after delivery and contact with the lesions respectively.

MECHANISM OF IMMUNITY IN VARICELLA-ZOSTER

The viruses from varicella and zoster present in vesicle fluid and after passage in tissue culture are both round and of the same size, about 225 mμ in diameter when examined in the electron microscope. The same cellular reaction is seen in the skin lesion in both conditions. It is characterized by giant multinucleated cells in the epidermal layer and typical acidophilic inclusions in the nuclei of the epithelial cells and the cells around the vessels in the corium. The secondary infiltration of inflammatory cells and the resulting pustule which usually appears in twenty-four to forty-eight hours in varicella may not, however, appear for three or four days in zoster. Varicella and zoster virus produce the same cytopathic effect in tissue cultures and grow in the same kinds of tissue. The behaviour of both viruses in tissue cultures is different from most other viruses in that infective virus is not released into the supernatant fluid from the infected cells (Weller, 1953). Some virus may be released by the rupture of infected cells by sonic vibration (Taylor-Robinson, 1959) but usually it is necessary to transfer some infected cells to the fresh culture to induce infection in them (Weller *et al.*, 1958). Presumably the virus passes from infected cells into adjacent fresh cells by cellular attachment or bridges. These characteristics of the virus may have some bearing on the pathogenesis of the disease and the mechanism of immunity in the natural host. It is possible that virus leaves the cell in a form which is rapidly killed outside the cell or in a non-infective form,

because the supernatant fluid although not containing infective virus contains complement-fixing (C.F.) antigen which is completely cross-reactive with convalescent sera from patients with either disease (Weller and Witton, 1955). Taylor-Robinson and his colleagues (Taylor-Robinson and Downie, 1959; Taylor-Robinson and Rondle, 1959) have found that C.F. and precipitating antibodies appear earlier and in higher titre in patients with zoster. This is what might be expected if one accepts the theory that the zoster element usually occurs in someone who has had varicella previously so that a basic or sensitized antibody-forming mechanism is already present when zoster occurs and an accelerated antibody response would be expected, with accompanying higher titre. As additional evidence of the close relationship, Weller and Coons (1954) used the fluorescent antibody technique on infected tissue culture cells and showed that labelled antibody from patients convalescent from either disease combined with either virus in the infected cells, and Weller and Witton (1955) demonstrated cross-neutralization with convalescent sera in tissue cultures.

DIFFERENTIAL DIAGNOSIS OF VARICELLA-ZOSTER

There is usually little question of a differential diagnosis in cases of chicken-pox but, if there is an atypical distribution of the rash or severe hæmorrhagic rash with or without pneumonia in an adult, the possibility of smallpox should be considered. Rapid laboratory tests for smallpox are now available to confirm the clinical diagnosis and a presumptive diagnosis may be available in an hour to twenty-four hours, depending upon the stage of the rash and the specimens that can be investigated. Giant multinucleated cells can usually be seen in smears from varicella lesions before the pustular stage but are not present in variola. Varicella and zoster do not produce lesions on the chorio-allantoic membrane (CAM) of the fertile hen egg but each of the pox viruses (variola, vaccinia and cowpox) produces a distinctive lesion within twenty-four to seventy-two hours. The lesions and symptoms of involvement of the geniculate or Gasserian ganglion with zoster virus, which may manifest themselves particularly after operation for trigeminal neuralgia, may be confused with those of herpes simplex, but the latter virus grows readily with distinct lesions on the CAM and infects suckling mice, whilst zoster does not. Occasionally, signs of motor paralysis have been present in patients with zoster; these may be due to zoster virus but the possibility of a simultaneous infection with poliomyelitis should be considered, and virological tests carried out.

TREATMENT AND CONTROL OF VARICELLA-ZOSTER

There is no specific measure that can be guaranteed to be of value for the control or treatment of either condition although claims have been made for convalescent serum, gamma-globulin, antibiotics, vitamins and various drugs. Chicken-pox is on the whole a benign, self-limiting disease except for occasional cases with pneumonia or encephalitis, and seldom gives cause for concern. Zoster on the other hand can cause very severe and pro-

tracted pain and strong sedatives may be necessary in addition to medicaments which will aid in rapid drying of the skin lesions. There has been a number of very severe and even fatal cases of varicella in patients who were receiving cortisone treatment for some other condition (Haggerty and Eley, 1956). Thus, the use of cortisone is contraindicated in patients with a rash in which there is a suspicion of varicella or zoster. There is some evidence that ultra-violet light has limited the spread of varicella in hospital wards and institutions.

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THE MEASLES VIRUS

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JUST two hundred years ago, in 1759, Francis Home described his experiments on immunization against measles.

'Considering how destructive this disease is, in some seasons;' he wrote, 'considering how many die, even in the mildest epidemical constitution; considering how it hurts the lungs and eyes; I thought I should do no small service to mankind, if I could render this disease more mild and safe, in the same way as the Turks have taught us to mitigate the small-pox'.

For his purpose he bound cotton swabs soaked with blood from an infectious patient into incisions made in a susceptible person. He was handicapped by great difficulty in finding subjects for inoculation but it seems that some of the individuals thus treated did develop measles. Now, in 1959, largely through the series of investigations of John Enders and his colleagues in America, vaccination against measles has been brought virtually within reach.

EARLY INVESTIGATIONS

Before describing these recent advances a brief account may be given of the work of other investigators of the present century.

In 1911, Goldberger and Anderson demonstrated that measles could be experimentally transmitted from man to monkey. Later, Blake and Trask (1921) confirmed this work and showed that intra-tracheal inoculation of filtered or unfiltered nasopharyngeal washings from measles patients produced in monkeys an illness closely resembling human measles. The animals developed a maculo-papular rash, catarrhal conjunctivitis and leucopenia. The infection was further transmissible by intratracheal injection of emulsions of skin and buccal mucosa or by intravenous injection of blood from infected animals. In 1938, Plotz reported the cultivation of measles virus in tissue cultures of minced chick embryo. He succeeded in propagating the agent for ten passages in tissue culture and demonstrated its presence by monkey inoculation with production of typical measles. Rake and Shaffer (1940) found that measles virus, obtained from the blood or pharyngeal washings of human cases, could be propagated by serial passage on the chorio-allantois of the chick embryo. Such egg-passage material when inoculated by various routes into susceptible children was shown by Stokes *et al.* (1943) to produce the typical reactions of very mild measles. In subsequent tests for immunity by exposure to measles or by challenging injections of blood from active cases it was found by Mar's *et al.* (1943) that a large majority of the children appeared to be completely or partially protected against the disease. The authors considered the results sufficiently encouraging to warrant further trial of measles virus, attenuated by egg-passage, for active immunization against measles.

ISOLATION OF MEASLES VIRUS IN PRIMATE TISSUE CULTURES

Cytopathic effects of the virus.—The work of Enders and Peebles (1954) marks the beginning of the modern period in the history of measles research. They described for the first time the successful isolation in primate tissue cultures of measles virus from blood and throat washings of patients and the cytopathic changes induced in them by its growth. The sequence of events was described by Enders (1956a) in the following words:—

'After we had shown that poliomyelitis could be cultivated in a variety of human

tissues the urge to try the same system with measles virus became irresistible, since in spite of intervening reports of its cultivation, none had been generally confirmed. Accordingly, with Peebles, we introduced into roller tube cultures of human kidney tissue blood or throat washings taken from typical cases during the first 24 hours of the rash. After a week or longer we found to our delight changes of a peculiar sort. As seen under low power these consisted of circumscribed areas in the cell outgrowth containing nuclei and cytoplasm but in which the cell boundaries had entirely disappeared. Upon continued incubation the cytoplasmic portion became increasingly vacuolated until it presented a torn or foamy appearance. In fixed and stained preparations these areas were seen to represent syncytia or large giant cells which contained 40 or more nuclei. Within most of the nuclei typical eosinophilic inclusion bodies were present. The process proceeds in a leisurely manner to involve ultimately the whole layer of newly grown cells . . . we believe that the virus which produces the effects in human renal cells we have described represents the etiologic agent of measles'.

Since 1954 abundant evidence has been adduced to substantiate his view: primary isolation from measles patients of agents producing typical cytopathic changes in human amnion or chorion cultures in England (Wright, 1957a), and in monkey or human kidney cultures in China (Tang *et al.*, 1958), Denmark (Bech and von Magnus, 1958) and the United States (Cohen *et al.*, 1955; Ruckle, 1957a). Isolation of the virus from the cerebrospinal fluid of encephalitis cases or from stools has also been reported.

Further propagation of the virus.—Reports of the passage of measles virus in other types of human cell cultures have also been made. For example, typical cytopathic changes have been observed in cell lines of heart, amnion, thyroid and Detroit-6 and in the malignant cell lines HeLa, KB and Hep-2. Growth in rodent kidney cultures has been reported by Wright (1957b), in a guinea-pig spleen cell line by Mascoli *et al.* (1959), and in an embryo rabbit kidney cell line by Enders *et al.* (1959).

SEROLOGICAL INVESTIGATIONS

Immunological response.—Studies of the immunological response following natural measles infection in human beings have been made by Enders and his colleagues (1957) and also by Ruckle and Rogers (1957). They have shown that both neutralizing and complement-fixing antibodies develop. The neutralizing antibodies are capable of inhibiting the development of the cytopathic changes induced by the agent in tissue cultures. The complement-fixing antibodies react with antigens prepared from the fluid medium of infected tissue cultures. Correlation was found to exist between the time when the two antibodies become detectable and also in their subsequent rise in titre and in their decline. Antibodies could be detected as early as twenty-four hours after the appearance of the rash and were present in the majority of sera obtained from twenty-four to ninety-six hours after its onset. The maximum titre occurred between eight days and two months. The titre declined gradually but antibodies were still detectable in the sera of a group of children who had had measles two or three years previously. Antibodies persist and were demonstrable in the sera of adults from various parts of the world who had had measles in childhood. Present evidence supports the view that agents isolated from measles patients are of antigenic

uniformity. A further point of interest established by Ruckle and Rogers (1957) is that early emergence of antibody terminates measles viræmia.

Diagnostic complement-fixation test.—Persons who have not had measles do not have complement-fixing antibody in their sera. Its early emergence in measles patients and rapid rise in titre suggest that the complement-fixation test could make a useful laboratory contribution to the diagnosis of measles when the clinical diagnosis may be in doubt. The necessary antigens can be procured commercially in the United States and a complement-fixation test can be undertaken in certain laboratories in Great Britain.

Antibody assay of gamma-globulin.—The newer techniques have made possible the assay for measles antibody content of human gamma-globulin or convalescent serum used for passive immunization (Ruckle and Rogers, 1957). This permits of greater precision than hitherto in the dosage of materials used for prevention or modification of the disease.

PATHOGENICITY FOR MONKEYS OF CULTURED MEASLES VIRUS

Serology of captive monkeys.—Early in their investigations on the pathogenicity of cultured measles virus Peebles and his colleagues (1957) found that the majority of normal monkeys resident for some time in their animal houses possessed circulating antibodies against the agent. By contrast sera taken from monkeys as soon as practicable after capture yielded negative serological results. It seemed possible therefore that measles had spread between the animal houses from the experimentally infected animals to the uninoculated members. Alternatively, since many monkeys have had a town life before capture they may have become naturally infected with measles and have introduced it to the animal houses with a resulting epizootic or enzootic. However this may be, the fact that many laboratory monkeys possess measles antibodies complicates their use as test animals for the presence of virus; it also gives reason to the variation in their susceptibility found by earlier workers.

Transmission of cultured measles virus.—In view of these serological findings Peebles and his colleagues (1957) selected for their transmission studies monkeys pre-tested for absence of circulating measles antibodies. They inoculated the animals by the intravenous or intranasal route with measles virus passaged in tissue culture. After an incubation period of nine to ten days there followed an illness in which might be noted a maculo-papular rash, measles viræmia, leucopenia and the emergence of specific complement-fixing and virus-neutralizing antibodies.

Simian agent.—Whether the causal agent of spontaneous measles infection of monkeys in captivity is the human virus or a closely related simian virus is a matter for further investigation. It is of interest in this connexion to note that Ruckle (1958) isolated from her uninoculated monkey kidney tissue cultures an agent which was indistinguishable by its cytopathic effects and antigenic attributes from human measles virus. It was considered by Peebles *et al.* (1957) that if the simian agent should prove to be a

separate entity and of lower pathogenicity for man than human measles virus it might be of use in the active immunization of human beings.

PATHOLOGY OF MEASLES

Post-mortem findings.—Histological examination of tissues taken post-mortem from measles cases dying in the pre-eruptive stage has revealed the presence of two types of multinucleate cells. Warthin-Finkeldy giant cells occur throughout the lymphoid tissue of the body. Fused epithelial cells are found in the bronchial mucosa and may form large sheets lying free in the bronchi; within these epithelial giant cells may be seen eosinophilic intranuclear and intracytoplasmic inclusion bodies.

Post-mortem isolation of virus.—The similarity of the histopathological picture at necropsy and the cytopathological changes in infected tissue cultures suggests that giant cell formation in the body is associated with the presence of measles virus. Work by Ruckle (1957b) supports this view.

She took organs at necropsy from a child who had died in the pre-eruptive stage of measles and prepared tissue cultures with them. In this way measles virus was grown from lung, spleen and cervical lymph nodes; histological sections from the body revealed the presence of giant cells in all these organs.

An agent indistinguishable from measles virus has been isolated from cases of giant cell pneumonia by McCarthy, Cheatham and Mitus (Enders, 1956b).

Giant cells in nasal discharge.—The occurrence of characteristic giant cells in the nasal discharge of patients in the prodromal stage of measles has been reported by Tompkins and Macaulay (1955) and by Haneke (1956). Control specimens from patients with upper respiratory tract infections of other causation gave negative results. The simplicity of the test and its possible usefulness in the early diagnosis of measles recommend its more extended investigation.

RELATIONSHIP BETWEEN MEASLES AND DOG DISTEMPER VIRUSES

Certain resemblances between the clinical manifestations and pathology of measles and dog distemper (Pinkerton *et al.*, 1945) led Adams and Imagawa (1957) to investigate the possible immunological relationship between their causal viruses. The results of their work suggest that the two viruses possess antigenic components in common. Thus, the cytopathic effects of measles virus in HeLa cell cultures were inhibited by distemper antiserum and, conversely, the pathogenicity for mice of distemper virus was neutralized by measles antiserum prepared in ferrets. Further, there occurred significant increases in neutralizing antibodies against distemper virus between acute- and convalescent-phase sera from measles patients.

PROPAGATION OF MEASLES VIRUS IN CHICK EMBRYO CELL CULTURES

The most promising approach to the production of a measles virus vaccine for human immunization lies in the recent work of Milovanovic *et al.* (1957)

and Katz *et al.* (1958) on the propagation of the virus in cultures of chick embryo cells. This work was preceded by two investigative stages:—

(1) First, a measles virus strain which had been passaged in human kidney cultures was adapted to growth in human amnion cultures. A change in the cytopathic effects became noticeable and, as well as the typical syncytial formation, there developed numbers of refractile, fusiform or stellate cells in which intranuclear inclusions were often found.

(2) The second step was the inoculation of the amniotic sac of the developing chick embryo with fluids from such infected human amnion cells. Serial passages were successful and the egg-adapted agent was confirmed as measles virus by appropriate tests. The final stage consisted of the growth of the egg-adapted measles virus in cell cultures of whole chick embryo; on passage the cytopathic changes associated with measles virus became apparent and eosinophilic intranuclear and intracytoplasmic inclusions were observed. The identity of the agent was confirmed in neutralization tests with measles antisera.

It is possible that fluids from chick embryo cell cultures infected with measles virus may provide material suitable for the preparation of a measles virus vaccine for human use. Inoculation into monkeys (Enders *et al.*, 1959) has, in fact, been shown to result in the production of neutralizing antibodies against measles virus. The developments which will doubtless follow are awaited with interest but the circumstance and occasion for active immunization against measles will require the most careful consideration.

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INTERFERON: THE PROSPECTS

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INTERFERON is a substance which shows in laboratory tests the behaviour one would expect of a wide-spectrum viral antibiotic. In this article an evaluation will be made of the prospects of its usefulness in viral infections of man and animals.

BACKGROUND

Interferon was found two-and-a-half years ago during a study of the virus interference phenomenon. It has been known for almost twenty-four years that one virus will interfere at the cellular level with the growth of many unrelated viruses. The first virus will interfere even when it has been rendered non-infective by heat or irradiation with ultra-violet light. It was not possible, however, to make any practical use of this finding since large doses of inactive virus may prove toxic, and also because the antigenic stimulus provided by the inactive virus would probably make it difficult to use the same material more than once.

Isaacs and Lindenmann (1957) demonstrated that when interfering virus is incubated with suitable cells there is formed in the cells and released into the medium a substance which can induce interference in fresh cells. This substance was called interferon and its antiviral behaviour closely resembles that of the interfering virus, but in other respects the interfering virus and interferon are quite different. For example, interferon is smaller than, and quite distinct from the virus serologically and is stable under acid conditions (pH 2) which inactivate the virus. It does not appear to have the two disadvantages mentioned above for inactive virus: i.e. interferon is relatively non-toxic for cells and it is either non-antigenic or very poorly antigenic. Quite apart from its theoretical interest therefore interferon is of potential practical interest as a chemotherapeutic agent.

PRODUCTION

The two main requirements for producing interferon are inactive virus and a suitable culture of cells. We have often used influenza virus inactivated by ultra-violet light incubated with whole-chick chorio-allantoic membranes suspended in a simple buffered salt solution. Interferon is produced in the cells lining the membrane and is liberated spontaneously into the suspending medium. Medium collected over the course of three days provides good starting material from which the interferon can then be concentrated and partially purified. This system was chosen for its convenience but it will be necessary to use different animal cells for experiments on the protective effect of interferon in infections in animals. Here, the experience gained in

manufacturing poliomyelitis vaccine from cultures of monkey kidney cells should be applicable to the manufacture of interferon on a large scale.

At the moment purification presents more of a problem than production. Interferon is a protein, a little smaller than serum antibody, and it may take some time before a protein of this size can be purified. The fact that it is prepared from cells incubated in a simple salt solution, however, means that the starting materials are not grossly impure.

ANTIVIRAL SPECTRUM *in vitro*

In our laboratory, interferon, prepared by incubating inactive influenza virus with chick chorio-allantoic membranes, inhibited *in vitro* the growth of the small-sized encephalitis viruses, medium-sized viruses of the influenza group and large viruses like vaccinia and cowpox. Ho and Enders (1959) have recently described a substance which they call virus inhibitory factor, which has properties very similar to those of interferon and which inhibits the growth of poliomyelitis and coxsackie viruses *in vitro*. In fact we do not know any animal virus which is not susceptible to interferon, but what has been observed is a striking variation among different viruses in their susceptibility to different doses of interferon. Thus, a dose of interferon which caused a slight reduction in the yield of fowl plague virus in chick fibroblasts completely suppressed all evidence of growth of West Nile virus in the same cells. In general the small encephalitis viruses seem to be very sensitive, many of the influenza and pox viruses are of intermediate sensitivity and fowl plague and herpes simplex viruses are more resistant to interferon. At present we have no idea what governs these differences in sensitivity.

DURATION OF RESISTANCE

In a recent series of experiments it was found that a single dose of interferon protected cells from infection with West Nile virus *in vitro* for most of the life-time of the cells (Isaacs and Westwood, 1959a). The cells were kept in a simple maintenance medium in which cell division was minimal and the medium was changed daily or every second day, so that any excess interferon was removed early in the experiment. Nevertheless the cells showed a prolonged resistance to infection with West Nile virus, probably because the interferon remained inside the cells. The resistance, however, could be broken down by providing the cells with nutrients which encourage cell division; presumably the interferon was diluted out as the cells divided until the intracellular concentration fell below that needed to protect the cells from virus action. In support of this suggestion, the resistance of the cells was largely maintained when further interferon was added along with the nutrients.

One could imagine therefore that in an infection *in vivo*, the amount of interferon needed to protect would depend upon the infecting virus, the number of susceptible cells exposed initially and the rate at which newly susceptible cells are being formed by cell division. Since most animal cells

do not divide more rapidly than once every twenty-four hours it might be sufficient to inject interferon daily or every second day during the treatment of a virus infection.

CELLULAR SPECIFICITY

Although interferon is active against a wide range of viruses, i.e. it has little specificity as regards the viruses, Tyrrell (1959) has drawn attention to an interesting cellular specificity effect. He found that interferon prepared in calf kidney cells was much more active when tested in these cells than when tested in chick fibroblasts; the converse is equally true. We have confirmed this finding by means of the technique devised by Porterfield (1959).

Porterfield showed that a culture of cells treated with a lethal dose of virus by the plaque method of Dulbecco (1952) could be protected from the destructive action of virus by interferon. To show this he used a modification of the antibiotic assay methods in current use: a cup containing interferon is placed in the centre of the plate and the interferon diffuses out and produces a zone of protected cells around it. In figure 1 are shown two plates treated with a large dose of Bunyamwera virus (one of the family of arthropod-borne viruses which includes yellow fever and dengue viruses). In the centre of the left-hand plate interferon prepared in chick cells has been placed, and a zone of protected cells has developed around the cup. In the right-hand plate, interferon prepared in rabbit kidney cultures has not protected the chick cells. The interferon prepared in rabbit kidney, however, was more effective than the chick material in protecting rabbits against intradermal infection with vaccinia virus (Isaacs and Westwood, 1959b). These results are in line with those of Tyrrell but it is not yet known how wide or how specific this effect is; indeed there is some preliminary evidence of cross-protection between calf and monkey cells. It is likely, however, that if interferon were required for experiments to protect man, it would have to be prepared in human cells or in cells of an animal close to man, e.g. monkey cells.

TOXICITY AND ANTIGENICITY

No systematic investigation of the toxicity of interferon has yet been reported, but all the indications are that it is of low toxicity. The zone of protected cells shown in figure 1 gives visual evidence of its lack of toxicity, and no cytopathic action was observed when we used doses of interferon much larger than those required to protect cells against destruction by virus. Interferon in doses which inhibited virus growth did not inhibit cell division; on the contrary, cell division may be enhanced under these conditions. It did not cause any inflammation when injected into the rabbit skin, and repeated injections of fairly large doses intravenously into rabbits in attempts to produce antibody, did not cause any obvious ill effects.

So far all attempts to produce neutralizing antibody to interferon by repeated injections of antigen plus adjuvants have failed in our laboratory and elsewhere. It is therefore either non-antigenic or very poorly antigenic.

This was an unexpected result but it is obviously important if interferon were to be used therapeutically, since it should be possible to protect animals frequently without the interferon rapidly losing its effectiveness.

ANIMAL EXPERIMENTS

Early animal experiments were carried out with interferon prepared in chick cells, before the cellular specificity effect described by Tyrrell was known. Interferon prepared in chick cells protected chick embryos against

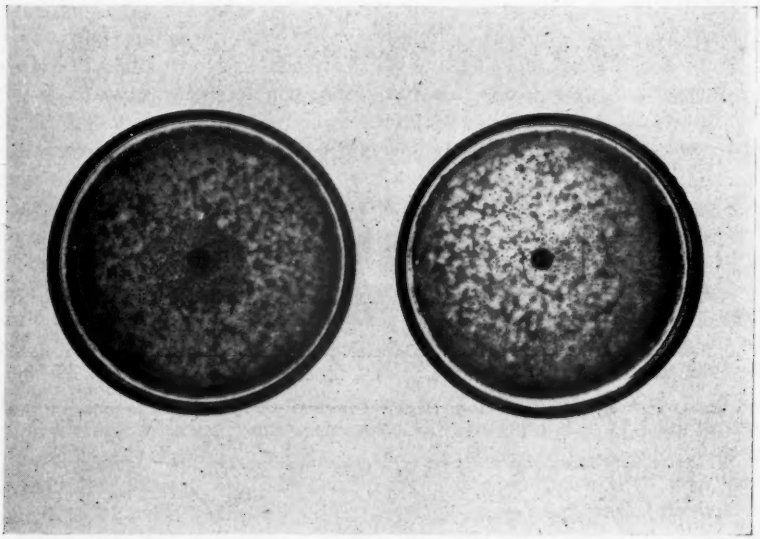

FIG. 1.—Two Petri dishes have been seeded with chick embryo fibroblasts and infected with sufficient Bunyamwera virus to destroy all cells. Immediately after infection the cells were overlaid with nutrient agar containing phenol red and a cup dipped in a preparation of interferon was placed in the centre. The cup in the left-hand plate contained interferon prepared in chick cells and a zone of cells protected from virus action has formed round the cup: no zone developed in the right-hand plate which contained interferon prepared in rabbit kidney cells. (Technique devised by Porterfield, 1959.)

infection with vaccinia virus but gave irregular protection against the same virus in the rabbit skin. Interferon prepared in rabbit cells, however, gave good protection in the rabbit skin.

When large doses of vaccinia virus were injected into the rabbit skin the interferon protected if it was given the day before the virus but not with it or after it. This finding had been expected from the results of similar experiments carried out *in vitro*. When small doses of vaccinia virus were used, however, protection was obtained from interferon given the day before or along with the virus. Presumably, the small dose of virus infects only a small number of cells initially, and these are probably not protected by the interferon but, by the time this small dose of virus has multiplied, the cells

in its neighbourhood will have acquired protection from the interferon. In natural infections the infecting dose is almost always small, so there is reason to hope that it may be possible to halt a virus infection in man or animals once it has started, but these experiments suggest that interferon would probably be more effective when given early rather than late in infection. The effectiveness of interferon is likely to depend upon the number of uninfected cells at the time the interferon is administered. At present there is no evidence that interferon can influence an established infection in a cell.

It is obviously important to try to protect other animals against different types of virus infection and this work is in progress at the moment. It is hoped that this work will lead via experiments in monkeys to attempts to protect man.

CLINICAL USE

The practical aim behind this work is to be able to protect man against virus infections. The difficulties at the moment are to produce large amounts of active material in human, or perhaps monkey, cells; to be sure that this material would not be toxic to man; and to find a convenient site of infection where the interferon could be rapidly and effectively applied. The respiratory infections seem to be a good first choice because the interferon can be applied directly to the nasopharynx. Systemic infections are more difficult because of the larger amounts of interferon required and because of the possibility that interferon might be attacked by proteolytic enzymes before it reached its required site of action.

Perhaps one of the most interesting lines of thought stems from the evidence that interferon is produced at a late stage of infection by a number of different viruses. It seems that interferon is normally produced as the infection is dying down, so that it may be that interferon is concerned in a natural mechanism of cellular resistance to virus infections. For example, the fact that people recover from colds in the absence of any clear evidence of specific immunity (Commission on Acute Respiratory Diseases, 1949) suggests that local cellular immunity may play a part. It would be encouraging if therapy with interferon were an extension of natural mechanisms of resistance to virus infection.

CONCLUSION

The prospects are beginning to look brighter but there is a great deal of work ahead and many pitfalls to be avoided before a laboratory wide-spectrum antibiotic can become a clinical antibiotic.

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INJURIES TO THE FINGER-TIP

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No portion of the human anatomy is so exposed to injury as the hand. And no part of the hand is wounded as often as the ends of the fingers. It is probably true to say that contemporary finger-tips are even more liable to damage than were those of bygone years. Sash windows, and all-too-collapsible deckchairs still exact their toll of incautious operators, but the doors of cars and railway carriages are commoner causes of injury today. The power-operated guillotines and the hydraulic presses of industry have in the past claimed many digits from the hands of those who tended them. But nowadays a man need not be a factory operative to jeopardize his fingers. Electrically driven saws can be very cheaply purchased by the amateur craftsman, who can, and often does, proceed to mutilate his hands in the privacy of his own garage. The 'Do it yourself' enthusiasts are exposed to other hazards besides this. 'Handyman's thumb'—the result of an inexpert but nevertheless, very forceful—hammer blow, is a very real clinical entity.

Because injuries to the finger-tips are so common, and because they often entail a long and painful period of incapacity for the patient, their correct treatment is a matter of great importance. Although the problems involved in treating, say, a badly crushed finger-tip would sometimes tax the judgment of an experienced plastic surgeon, yet, in the nature of things, the individual faced with such a case is more often than not a general practitioner or a junior house surgeon. The purpose of this article is to describe some of the most commonly seen injuries of the distal segment of the finger, and to suggest simple methods of treatment calculated to yield serviceable digits in the shortest possible time. Infected lesions, and those involving tendons (except the terminal portion of the extensor tendon), have been regarded as falling outside the scope of the present article, and are not discussed.

CLASSIFICATION

The following scheme will be found a convenient one for classifying injuries, not only of the finger-tips, but of the rest of the hand as well:—

(A) Minor closed injuries: e.g. subungual hæmatoma.

(B) Minor open injuries: e.g. cuts and puncture-wounds.

(C) Serious but 'tidy' lesions: this group comprises all those cases in which some important tissue, deep to the skin, has been damaged, as well as all those in which part of the digit has been amputated. The wound, however, has been from some instrument which has divided the tissues cleanly without much crushing or laceration.

(D) Serious and 'untidy' lesions: those cases in which substantial damage

has been inflicted by crushing, or by the movement of an irregular surface against the finger, so that there has been abrasion and irregular tearing of the tissues.

MINOR CLOSED INJURIES

The commonest example of this type is the *subungual hæmatoma*. Whenever such a hæmatoma is seen, radiographs of the subjacent phalanx are usually ordered. This is advisable on medico-legal grounds, but the demonstration of such a fracture does not, in fact, determine the subsequent treatment of a given case. This relates rather to the size of the hæmatoma. A small one, not causing much discomfort, can be left, A larger one, particularly if associated with severe pain, should be drained by drilling a hole in the nail. A dental burr is the ideal instrument for this, but a sharp trocar, with its point resting on the nail, and twirled between finger and thumb, serves almost as well. When the nail is partially detached, or is 'floating', it is best removed *in toto*, under a digital nerve-block. A large laceration of the nail-bed is always thereby exposed. If this gapes, one or two sutures of thin catgut can be used to close it, and will not subsequently require to be removed. When in doubt, it is sound practice to err on the radical side and avulse the nail.

FIG. 1.—The typical 'mallet-finger' deformity.

The most commonly encountered tendon injury in the hand is that which produces a '*mallet finger*'. In this condition the patient loses the ability to extend fully the distal interphalangeal joint, and the tip of the finger drops into flexion (fig. 1). The cause of the deformity is an avulsion of the extensor tendon from its insertion on the distal phalanx: sometimes the substance of the tendon yields (particularly if it is the site of a degenerative process), sometimes the actual bony insertion is broken off. There may be a history of some violence which suddenly flexed the finger-tip—as in the stopping of a fast ball in cricket. At least as often the patient describes only a sudden pain during some trivial strain; in such circumstances one can postulate a pre-existing weakness of the tendon over an arthritic joint.

A 'mallet' deformity is commonly treated by the application of a plaster cylinder to the finger, with the last joint held in hyperextension. If this position, in which the damaged surfaces are in apposition and the tendon relaxed, can be maintained for some six weeks, healing may theoretically

occur. Such a cast, however, seldom remains comfortable or secure for so long. At the best, it softens at the end and fails to immobilize the finger-tip. At the worst, it gives rise to a pressure sore on the dorsum of the finger. Because the initial pain and swelling subside after a few weeks and leave a perfectly useful, albeit slightly bent, finger, many people need only an explanation of the injury, and reassurance. But if the patient with a 'mallet finger' is not prepared to accept the trivial deformity that ensues in an untreated case, operation under a local anæsthetic is indicated. A Kirschner wire is drilled across the distal joint, while it is held in hyper-extension. Then, when radiographs have confirmed a satisfactory position, the wire is cut off at the skin surface. Neither this treatment, however, nor the exposure and suture of the tendon, carries a guarantee of success. Some stiffness or deformity is common after both procedures, but as has been indicated, neither event involves any permanent impairment of the hand's function.

MINOR OPEN WOUNDS

These are the trivial injuries for which treatment at home, or at a works first-aid post, often suffices. When the wound is severe enough to demand more skilled attention, the doctor who sees it should bear one or two points in mind. The blood supply of the fingers is very rich, and the viability of the tissues not easily impaired. Therefore only very dirty wounds call for any excision, and that a cautious one. Because the skin is bound down by fibrous septa at the finger-tip, wounds here do not gape widely. Suturing should be restricted to a minimum number of stitches, or there is a risk of 'sealing in' infection.

When examining a deep gash across the pulp of the finger, it must be remembered that such an injury can sever the insertion of the flexor digitorum profundus. Failure to notice this lesion is particularly unfortunate inasmuch as the condition is ideally treated by primary suture, using stainless steel wire.

Minute particles of metal, sewing machine needle-tips and the like, buried in the finger-tip, are best left *in situ*. Their removal often entails an extensive dissection, which leaves the member badly scarred, and hypersensitive. Foreign bodies which continue to cause real discomfort should be removed by an elective procedure, conducted in a bloodless field, and through a carefully considered incision.

Puncture wounds call for no particular treatment in the ordinary way, but when a puncture has been inflicted by an object strongly suspected of being septic—such as a soiled scalpel—it should be incised in cruciate fashion. The 'points' of the crossed incision can then be snipped off to allow free drainage, and an appropriate antibiotic administered.

SEVERE BUT 'TIDY' INJURIES

Metal and paper guillotines, high-speed saws with fine teeth, and occasionally heavy, or mechanically actuated, doors, are typically responsible for these

injuries (fig. 2). Such agents effect a clean section of the finger, and the lesions differ from each other only as regards the level of the amputation, and whether it has taken place at right-angles to the long axis of the finger or obliquely. In the management of these injuries, two commonly practised courses are to be condemned. In the first place, simply applying some such dressing as 'tulle gras' to the stump, and leaving it to heal from the edges,

(a) (b)

FIG. 2.—Guillotine injury (a), and its repair by a full-thickness skin graft (b).

is insufficient. Infection will occur, healing will be very slow and an adherent tender scar will result. Only in the case of small children, in whom rapid skin regeneration occurs, or in those stumps which have been neglected, and which are already infected, is such a policy permissible. Nor should re-amputation of the distal phalanx, to allow of skin flaps being formed, be advised. Easy closure and rapid healing are obtained by such a method at the cost of a valuable half-inch or more of finger length. On the other hand, however, when a skin flap has been created by the injury—where, in other words, the finger-tip has been amputated in an oblique plane—it is permissible to nibble away a little of any exposed bone, to permit of this flap being turned down and used to cover the stump. The application of a graft to such a flap would yield a flabby tapering finger-tip of poor appearance and function.

What then, should be done to close clean, traumatic, amputations of the fingers? The techniques most often employed utilize free skin grafts or

flaps derived from unwounded areas of the same hand. Free grafts may be cut from the forearm, and consist of the whole thickness of the skin (fig. 2), or part of it. The latter type of graft is easily obtained, 'takes' well, and presents no problem as regards the donor area. Full-thickness grafts require rather more skill. They 'take' less certainly than split-thickness grafts, and leave a skin defect at the donor site which, in turn, requires

(a) (b)

FIG. 3.—Injury from a wood-working machine (a), and its repair using a thenar flap (b).

grafting or suturing. They have, however, one notable advantage over the thinner grafts. They replace much more adequately the normal skin of areas, such as the front of the index finger-tip, which are exposed to much stress. In the case of both grafts, given a suitable recipient site, success depends upon their being accurately sutured over the defective area under slight tension. Silk sutures are used, and they should be evenly spaced around the whole circumference at very small intervals. If necessary, holes can be pierced through a nail-edge, or a nail bed, to take them. The ends of the sutures are left long, and used to tie a pressure dressing—e.g. of cotton pledgets wrung out of proflavine emulsion—over the wound. Once firmly stitched in position, the graft is left undisturbed and uninspected for eight to ten days.

Not all skin defects at the finger-tip can be repaired by free skin grafts. Sometimes a raw bony surface has been exposed, on which such a graft

will not flourish. Sometimes the volar pad of soft tissue has been lost, and a graft composed only of skin will not adequately replace it. In such circumstances the use of a 'flap' is indicated. It may be possible, for instance, to flex the damaged finger until its end touches the thenar eminence (fig. 3). A skin flap is then dissected up from this region, and, while still attached at its proximal end, it is firmly sewn over the raw area. The site, and base of, the flap are invested with a split skin graft, and the hand bandaged up, with the fingers flexed, for a period of ten to fourteen days. Then the base of the flap is transected, and the fingers straightened, and dressed in the usual way. In a recent article Flatt (1957) has described the practical details of this operation. The skin flap can sometimes be raised in the same manner from the lateral aspect of an adjacent finger: this is a particularly useful method of repairing the tip of the thumb. The surgeon essaying these 'flap' operations for the first time may feel apprehensive, lest the patient's hand should become permanently stiffened during the period of immobilization. In fact, it is most unusual for any serious stiffness to develop in the young or middle-aged worker who is the commonest subject for such operations. The procedure is, of course, contraindicated in old or arthritic patients. Nor should it be performed on any manual worker who has greatly thickened or calloused skin at the proposed donor site. Such horny material lends itself poorly to plastic procedures.

FIG. 4.—Crushing injury from a steam-heated clothes press. Amputation is the only feasible treatment, but grafting the stumps will minimize the mutilation involved.

One other group of finger-tip injuries can conveniently be considered under the present heading. It is that in which amputation has not been quite complete, or in which the detached fragment has been preserved. No hard and fast rules can be laid down about such cases, but when the patient presents with an all but amputated finger-tip dangling from his hand, or produces the severed member from his pocket handkerchief, it should be clearly explained to him that the mere replacement of such a fragment, though sometimes a justifiable experiment, is more often than not a failure. That it is justifiable is proved by the occasional survival of a fragment which is so large that it includes the whole nail-bearing area. The finger-tip

in these cases should be held in position with a minimum of sutures, passing through the skin edges only. A dressing, or light plaster cast, is then applied in such a way as to permit inspection of the tip. If, after forty-eight hours, this is obviously discoloured, the loose fragment should be removed and a graft applied to the stump.

When the chances of the reposed tissues surviving seem slight—because they are lacerated or soiled, or because the fragment is too large—they can often be dissected to furnish full-thickness grafts for dressing the damaged finger.

SEVERE AND 'UNTIDY' INJURIES

These injuries, commonly due to crushing (fig. 4), are amongst the most difficult of all to treat. They often involve more than one digit, they are excruciatingly painful (as distinct from guillotine injuries) and they may be associated with considerable shock. The accidents responsible for them include the unexpected slamming of heavy doors, or of the steel hatches found on ships and railway engines: misdirected hammer blows: and the malfunction of a wide range of machine tools, lathes and power presses.

The tip of a finger injured in such a way (fig. 4) is often shredded, with fragments of nail and terminal phalanx discernible among pieces of tattered skin. Each case must be considered on its own merits, but, in general, conservative measures have less justification in these cases than in the rest of hand surgery. The stitching together of several tags of devitalized skin over a crushed terminal phalanx only destines the patient to a long painful period of incapacity, and leaves him with a distorted tender finger when healing eventually occurs. Amputation through sound tissue—making very sparing use of any surviving skin flaps, and more often obtaining wound closure with free grafts—is not only the most expedient, but often the most beneficial treatment.

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SULPHAMETHOXYPYRIDAZINE IN THE TREATMENT OF RESPIRATORY INFECTIONS IN CHILDREN

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THE recent introduction of a long-acting sulphonamide, sulphamethoxypyridazine, has aroused fresh interest in this group of drugs.

PHARMACOLOGY

Reports of clinical trials with this drug from the United States indicate that therapeutic blood levels are maintained with a single daily dose, and that there is a low incidence of toxic effects (Boger *et al.*, 1956; Frisk and Wassen, 1957). Sulphamethoxypyridazine is rapidly absorbed from the gastrointestinal tract and very slowly excreted by the kidney. As a result, therapeutic blood levels (i.e. 10 mg. per cent.) are quickly reached and maintained with one daily dose. Less than 5 per cent. of the sulphamethoxypyridazine is acetylated but the acetyl form has a low urinary solubility. This is a theoretical source of renal complication. The antibacterial activity of sulphamethoxypyridazine has been shown to be equivalent to that of sulphadiazine (Maren and Mayer, 1957).

The advantages of a single daily dose and the low incidence of toxic effects make this drug useful in children. Reports of its use in pædiatrics are few and no direct comparison has previously been made with the better-known sulphonamides. In this controlled clinical trial, sulphamethoxypyridazine has been directly compared with sulphadimidine in the treatment of bacterial respiratory infections in children. Particular attention has been paid to the incidence of toxic effects.

SCOPE OF INVESTIGATION

Methods and material.—For a period of six months patients admitted to the medical ward of the Royal Belfast Hospital for Sick Children suffering from lobar pneumonia, broncho-pneumonia, bronchitis and tonsillitis were admitted to the trial. The usual diagnostic criteria were applied and the diagnosis in all cases was primarily a clinical one. In the final analysis, no attempt was made to differentiate between lobar pneumonia and broncho-pneumonia; a difficult problem particularly in younger children, even with the aid of chest radiographs, which were not taken routinely in this trial. Those children too ill for treatment with sulphonamides alone, and those who had received any antibiotic or chemotherapy before admission to hospital, were excluded from the trial. The doctor in charge had complete freedom to alter the treatment of any child at any time.

Dosage schedule.—As children were admitted to the ward they were allocated, in strict rotation, to one or other of two groups:—

(i) *Group S*—Children treated with sulphadimidine. These children were given 80 mg. per pound (173 mg. per kg.) body weight per twenty-four hours, after a loading dose of 40 mg. per pound (88 mg. per kg.). Therapy was continued for a minimum of five days.

(ii) *Group K*—Children treated with sulphamethoxypyridazine. These children were given 5 mg. per pound (11 mg. per kg.) body weight per twenty-four hours after a loading dose of 10 mg. per pound (22 mg. per kg.) body weight. As with Group S, therapy was continued for a minimum period of five days. The dosage of sulphamethoxypyridazine was based on information derived from the earlier clinical trials. To confirm that this dosage was effective, a small series of blood-level estimations was undertaken. This showed that therapeutic blood levels were rapidly achieved and maintained with this dosage. More recent work has shown that effective blood levels are maintained with the smaller daily dose of 3 mg. per pound (6.5 mg. per kg.) body weight per twenty-four hours, after a loading dose of 6 mg. per pound (13 mg. per kg.) body weight (Nichols and Finland, 1957).

Group comparability	Group K	Group S
Males	17	18
Females	14	12
Age:		
0-2 years	18	17
Over 2 years	13	13
Mean age	3.2 years	3.7 years
Disease:		
Pneumonia	16	11
Bronchitis	12	17
Tonsillitis	3	2
Mean temperature on admission	100.8°F. (38.2°C.)	100.7°F. (38.2°C.)

TABLE I.—Comparison of two clinical trial groups.

Investigations:—On admission and before treatment was started, the following investigations were undertaken: (i) throat swab, (ii) a specimen of urine was examined for red blood cells, albumin and crystals, and (iii) hæmoglobin, white cell count and platelet count. These investigations were repeated twenty-four hours after sulphonamide therapy had been stopped.

The assessment of clinical progress is difficult to standardize. In this trial, an attempt was made to reduce subjective impressions by using a detailed record sheet on which changes in the listed physical signs and symptoms were recorded daily by the same observer throughout the trial.

Diagnosis.—In all cases the diagnosis was a clinical one, although often confirmed by chest radiographs. Attempts to effect a bacteriological diagnosis by means of throat swabs were unsuccessful.

Clinical trial.—Originally 139 children were included in the trial, 61 of whom were judged eligible. Of those rejected, 57 had received some form of antibiotic or chemotherapy before admission to hospital; 14 children were considered too ill for treatment with sulphonamides alone and seven children who required additional antibiotic therapy (of whom three were in Group S and four in Group K) were also rejected. There were 30 children in group S (those treated with sulphadimidine) and 31 children in group K

(those treated with sulphamethoxypyridazine). Table I shows that the two groups were comparable with regard to sex, age and mean temperature on admission.

RESULTS

Table II sets out the results of treatment in the two groups. The criterion of a normal temperature was that it should remain under 99°F. (37.2°C.) for

Results of treatment	Group K	Group S
Temperature:		
No. normal after 3 days	11 (35%)	5 (15%)
No. normal after 6 days	25 (81%)	25 (89%)
Mean day temperature normal	3·5	3·9
Physical signs:		
Clear after 3 days	11 (36%)	10 (37%)
Clear after 6 days	26 (86%)	28 (94%)
Mean day clear	4·2	4·1
Mean hospital stay in days	8·3	7·9

TABLE II.—Results of treatment with sulphamethoxypyridazine (group K) and with sulphadimidine (group S).

twenty-four hours. The lungs were considered clear when all abnormal physical signs had disappeared, except for bronchospasm which persisted in nine children in group S, and in five in group K. There was no difference in the rate of recovery between the two groups, in spite of the slightly higher

Toxic effects	Group K (31 children)	Group S (30 children)
Nausea	0	2
Vomiting	1 (3%)	9 (30%)
Rashes	0	0
Crystalluria	0	2
Hæmaturia	1	1
Headache	0	0
Total no. with toxic effects	2 (6%)	12 (40%)

TABLE III.—Incidence of toxic effects in children treated with sulphamethoxypyridazine (group K) and with sulphadimidine (group S).

incidence of pneumonia in group K. The mean duration of the fever, the recovery rate and the mean stay in hospital were similar in each group. In all but eight children, five days' treatment was effective. These eight children were divided equally between the two treatment groups. The four children in group S needed an average of seven days' therapy, those in group K an average of eight days. No patient in either group needed more than eight days' treatment with sulphonamides.

From these results it is concluded that sulphamethoxypyridazine is as effective as sulphadimidine in the treatment of this group of diseases in children.

TOXICITY

Table III sets out the incidence of toxic effects in each group and illustrates the differences between them in this respect. In group S, one child developed

sulphadimidine crystalluria, and another child developed this complication in association with microscopic hæmaturia, both having received five days' treatment. In group K, no children developed crystalluria and one developed microscopic hæmaturia. In all these children, no other untoward effects were noted; the urine in each case returned to normal three days after sulphonamide therapy was discontinued.

The principal difference between the two groups was in the more frequent occurrence of vomiting in group S. Vomiting due to the sulphonamide was said to be present when it occurred on more than half the treatment days. By this definition, 10 children in group S vomited as a result of treatment with sulphadimidine. In group K, only one child vomited as the result of treatment with sulphamethoxypyridazine. A closer examination of these figures showed that all but two of the children in group S who vomited were under 2 years of age and received the sulphadimidine in the form of a flavoured suspension. In older children who received sulphadimidine in this form, there was no nausea or vomiting. In the one instance of vomiting in group K, the sulphamethoxypyridazine was given in tablet form. No other toxic effects were noted in either group. The hæmatological examinations before and after treatment showed no significant changes in either group.

DISCUSSION

The difficulty in finding children who have not received some form of antibiotic or chemotherapy before admission to hospital was the reason why the numbers in the trial were relatively small. As stated, 57 out of 139 children were rejected on this account compared with 21 rejected because of the severity of their illness, or the need for additional therapy. Attempts to make a bacteriological diagnosis by means of the throat swab demonstrated again how unreliable this method is in children; this is in agreement with Fisher and Whitfield (1952).

Sulphonamide crystalluria did not occur with sulphamethoxypyridazine whereas it was noted on two occasions with sulphadimidine. When crystalluria occurred there were no other serious renal effects, the urinary output was not noticeably reduced and three days after stopping sulphadimidine therapy the urine was normal. One case of microscopic hæmaturia was recorded in each group. In a recent review of 29 cases of crystalluria and hæmaturia caused by sulphonamides in children, Arneil (1958) reported only one instance in which crystalluria resulted from the administration of sulphadimidine. This particular child had been given 200 mg. per kg. body weight per day: a dosage comparable with that used in the present trial. No other ill-effects were reported. It would appear that even in this dosage range crystalluria may occur. So far no cases of crystalluria occurring in patients receiving sulphamethoxypyridazine have been seen in this hospital.

Vomiting was more common in children treated with sulphadimidine. It usually occurred in children under 2 years of age who received the drug as a flavoured suspension. Vomiting is a common symptom of tonsillitis,

but surprisingly it was seen in only one of the five children suffering from this disease in this trial (this child was treated with sulphadimidine). The vomiting may have been related to some constituent of the suspension other than the sulphadimidine but, whatever the precise cause, only 3 per cent. of the children treated with sulphamethoxypyridazine vomited as a result, compared with the 30 per cent. so affected in the sulphadimidine group.

Another advantage enjoyed by sulphamethoxypyridazine is its ability to maintain effective blood levels with a single daily dose. This saves time on the part of the nursing staff and in itself possibly contributes to the lower incidence of such side-effects as nausea and vomiting; children will tolerate medicine given once a day better than medicine given four times a day. The cost of treatment with either of these drugs is small compared with that of the antibiotics. It is reassuring that no serious toxic effects were seen with either sulphadimidine or sulphamethoxypyridazine.

This trial was undertaken to find out how sulphamethoxypyridazine compared with sulphadimidine in the treatment of certain respiratory infections in children. From the results, in view of the comparability of the two treatment groups, it is suggested that sulphamethoxypyridazine is as effective as sulphadimidine, that one dose a day is effective and that the incidence of toxic effects is lower with this drug than with sulphadimidine.

SUMMARY

A new long-acting sulphonamide—sulphamethoxypyridazine—has been compared with sulphadimidine in the treatment of 61 children with respiratory infections.

The results of treatment have been assessed in two comparable groups of children.

It is considered that sulphamethoxypyridazine is as effective as sulphadimidine in the treatment of bacterial respiratory disease in children and that toxic effects are less common with the former drug.

I wish to thank Professor F. M. B. Allen and Dr. W. A. B. Campbell for their advice and encouragement, and the medical and nursing staffs of the Royal Belfast Hospital for Sick Children for their wholehearted cooperation in carrying out this trial.

I am also grateful for the help given me by Mr. Thomas McFarland, F.I.M.L.T., in carrying out the sulphonamide estimations. The sulphamethoxypyridazine ('lederkyn') used in this trial was generously supplied by Mr. J. R. Wilson, F.R.C.S., Medical Director, Lederle Laboratories Division, Cyanamid of Great Britain Ltd.

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LIQUID PROTEIN CONCENTRATE IN CLINICAL PRACTICE

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In health the digestive system breaks down the proteins of the food into amino-acids which are absorbed for synthesis into tissue protein. The average adult requirement is about 50 grammes of animal protein a day. Should the caloric intake of the body be inadequate, this requirement of protein is met by breakdown of tissue protein. During many diseases, and after surgical operations, such tissue breakdown takes place to supply the immediate metabolic needs, and the protein loss must be made up by extra protein intake during convalescence.

Unfortunately, in many diseases and often after operations, the digestion of proteins is impaired, or food intake is restricted, just at the time when the needs of the tissues are increased. In an attempt to solve this problem various protein extracts or supplements have been utilized in recent years with varying degrees of success. The ideal substance would be one which required no digestion, which was easily soluble in water, contained all essential amino-acids, did not disturb the blood pH or the electrolyte balance of the blood, and was reasonably palatable; if it could be sterilized, buffered and rendered fit for intravenous administration, this would be an additional advantage. Such an ideal has not yet been attained, but there has been considerable progress in this direction. Preparations of casein, or its immediate breakdown products, prepared from milk, have been used clinically for nearly twenty years, but they do not give a very well-balanced mixture of amino-acids, and they require a considerable amount of breakdown in the digestive tract before they can be absorbed; some of them also have a strongly 'cheesy' flavour, and rather limited solubility.

Two years ago, we instituted a clinical trial of a liquid protein concentrate, which seemed to be an improvement upon the various casein preparations which were available, and have now used it in a variety of clinical conditions.

CONSTITUTION OF CONCENTRATE

The protein concentrate consists of a saturated aqueous solution of amino-acids and simple peptides, with some naturally occurring members of the

vitamin B complex. The inorganic fraction contains sodium and potassium as cations, with phosphate and chloride as anions. The amino-acids include the essential amino-acids, and 40 per cent. of the total protein nitrogen is contained in the amino-acids. The relative concentrations of the various amino-acids present in the free state show a remarkable similarity to those of digested serum proteins, as is well seen in the accompanying chromatogram (fig. 1).

APPLICATION IN MEDICINE

The possible field of application of any protein extract is obviously very wide. This extract has been used in five groups of medical conditions:—

(1) Malnutrition in elderly patients
(2) Malabsorption states
(3) Hypoproteinæmia
(4) Œsophageal obstruction
(5) Cachexia from neoplasm

The patients with malnutrition were elderly patients admitted to a geriatric unit, who had been living alone on a very deficient diet consisting mainly of bread, jam and tea. A depleted serum protein level was often present, with clinical signs of multiple vitamin deficiency in addition to loss of weight. Many of the patients were edentulous and had no dentures. They were given a soft normal diet and 2 to 3 ounces (60 to 80 ml.) of protein concentrate daily. Not only was the rate of gain in weight improved by the addition of the protein extract, but the serum protein was restored to normal levels within about two weeks instead of in a month. An unexpected feature in several of the patients was a striking improvement in appetite. Vitamin deficiencies were corrected by administration of appropriate vitamins, and iron was given intramuscularly to patients with a hypochromic anæmia. Of the first 10 patients treated with the extract, only one did not tolerate the flavour and stopped it before completing two weeks' treatment. Several patients said it tasted either like yeast or a little fishy, but they did not object to taking it, and completed a course of three to four weeks on it.

Malabsorption states offer a variety of dietetic and therapeutic problems, and this group of patients included two with steatorrhœa and four with marked loss of weight and poor nutrition after partial gastrectomy. All of them were helped by the addition of the extract; in the post-gastrectomy patients, the small bulk of the extract was of particular advantage, as they could not tolerate bulky meals. The flavour of the extract caused distaste in four of these patients on continued administration, but intermittent use has helped them to maintain an improved nutritional state for over six months.

Two patients with hypoproteinæmia secondary to chronic nephritis of the 'nephrotic' type with plasma protein below 5 g. per cent. were given the extract when they were unable to take sufficient protein on a high-protein diet. With this addition the plasma protein rose to 5.6 g. per cent. and 6 g. per cent. respectively and the œdema was controlled.

Three patients with malignant œsophageal stricture which permitted only a fluid diet, were given the extract as a supplement and two of them showed a

temporary gain in weight, with alleviation of the feeling of weakness. One of the patients had an exploratory operation and a gastrostomy and then nutrition was maintained via the gastrostomy for three months, using protein extract as the main source of protein, until tracheal compression

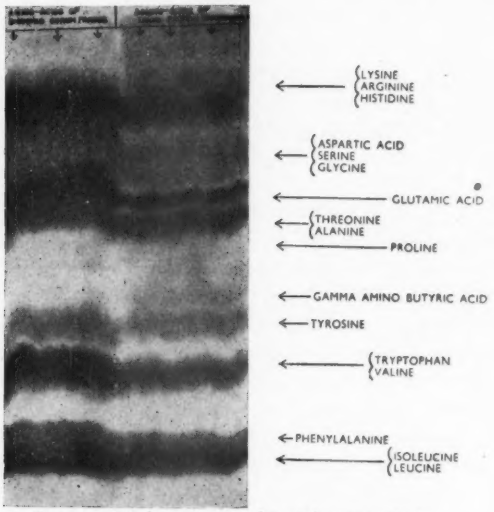

FIG. 1.—Chromatogram of protein concentrate.

terminated the picture. The use of protein extract appears to offer a method of correcting the nutritional deficiency of these patients quickly to prepare them for a surgical attack on the œsophageal stricture.

Cachexia in malignant disease is by no means completely understood, but increased metabolism by the neoplastic tissue, interference with the normal body metabolic processes and impairment of appetite all contribute to it. In non-alimentary neoplasms the addition of protein extract to the diet has produced some improvement in appetite, and some temporary weight gain in several patients, including patients with advanced bronchial carcinoma, ovarian carcinoma and sarcoma.

APPLICATIONS IN SURGERY

The applications of a protein concentrate are not so numerous in surgery as those available in medical practice, but there are definite conditions in which the use of a protein concentrate can be beneficial. The liquid protein concentrate has been studied from the point of view of its applications in the acute surgical ward. The following conditions were chosen for treatment:—

(1) Ulcerative colitis with ileostomy.
(2) Rehabilitation after surgery in cases of carcinoma of the colon and rectum.
(3) The immediate postoperative treatment in cases of neoplasia.
(4) Tube feeding for gastrostomy and jejunostomy or after resection of carcinoma of the œsophagus.

Two patients with severe ulcerative colitis requiring total colectomy and ileostomy have had a prolonged course of the liquid protein concentrate. Both patients gained weight and there was an improvement in appetite. After six to eight weeks' continuous treatment the patients became nauseated by the taste, but after a short rest and a slightly reduced dosage, they were able to continue for a further three to four weeks.

In the second group, two patients were treated—both successfully. The most notable clinical feature was a more rapid weight gain. It was noticed in this condition that the dose has to be watched, as overdosage could interfere with the tolerance of the colostomy. There is a natural tendency with substances such as this to overdose rather than underdose. A small dose can be very beneficial and well tolerated.

The third group is rather more difficult to assess. All patients with malignant disease have excess protein loss, and those patients who have been unable to take extra protein were found to respond to the use of the liquid protein concentrate. The prolonged use which is often necessary in this class of patient proved intolerable to some. In this third group could be included patients who are admitted to the hospital with a surgical emergency requiring immediate treatment but who are grossly underweight and undernourished. These patients have shown the best response of all to the liquid protein concentrate.

In the fourth set of conditions the preparation proved effective, particularly in gastrostomy and jejunostomy feeds. An attempt was made at the Liverpool Thoracic Centre to access its usefulness in carcinoma of the œsophagus. Unfortunately, the mortality is high in these cases whatever the treatment, and it was found that a very large series would be necessary in order to assess the substance fully, and this would need to extend over some years. The following points, however, did emerge clearly from the small series studied: (1) The clinical response with the liquid protein concentrate was as satisfactory as with any protein used hitherto. (2) It proved more suitable than the other proteins for continuous drip through a Ryle's tube. (3) It was found suitable for administration to patients with an œsophageal stricture or in the immediate postoperative period with the tube dwelling in the duodenum.

APPLICATIONS IN PSYCHIATRIC MEDICINE

In psychiatry there is a tendency for subclinical nutritional deficiency states to be overlooked, especially in the elderly senile group. The nutritional requirements of the acute patients are better attended to. In the alcoholic and acute toxic confusional states the problem of supplying a small-volume concentrated diet rich in protein in the early stages is often a matter of urgency, whether these patients are nursed in their homes or in hospital.

With a view to assessing the value of this preparation, a small number of patients who were undergoing insulin coma treatment were interrupted in the hypoglycæmic coma stage with tube feeds of liquid protein concentrate,

and the effect on the level of coma and the blood sugar was noted. It was found that in some the protein concentrate was as efficient in causing return to consciousness as the glucose solution normally used. In most of this group small protein feeds subsequently prevented relapses into coma, but

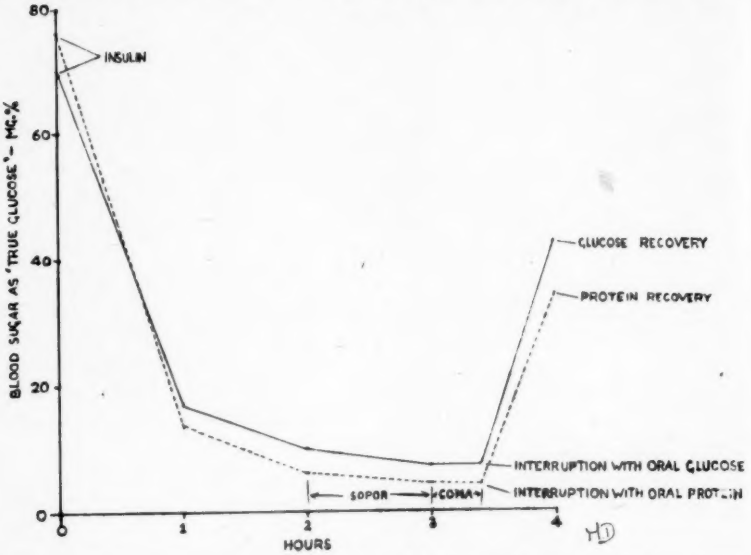

FIG. 2.—Blood sugar response to administration of (a) glucose, (b) liquid protein concentrate.

in some small additions of glucose to the solution were required. In the protein-only patients, the increase in blood sugar was not so marked as that associated with glucose feeds (fig. 2), and the amino-acids in the serum were significantly increased. The patients also tended to be calmer after the protein interruption. Due to the large doses used, however, vomiting sometimes followed and occasionally diarrhœa. This investigation shows that the amino-acids of the protein concentrate are rapidly absorbed and rapidly metabolized. The reservoir of amino-acids established in the blood was drawn upon to maintain an adequate level of glucose for cerebral metabolism.

The preparation was also tried out in debilitated patients, with excellent results: in outpatients in whom anorexia was a prominent symptom, there was a rapid improvement in appetite, weight gain and general nutrition. The improvement began as soon as the patients started the treatment, and the weight gain was substantial.

In other patients in whom the mental illness was associated with liver dysfunction and low serum proteins, there was a rapid return of these to normal. The vomiting and diarrhœa which occurred in the insulin group did not occur in any of the other patients who were on a smaller dose.

The general experience suggests that the preparation is capable of

replacing the more bulky and heterogeneous mixtures generally used to correct low-protein intakes associated with certain psychiatric disorders, and that in cases of severe deficiencies it can be life-saving, though in these cases preparations of high vitamin potency are naturally also required.

TUBERCULOSIS

It is difficult to assess the value of protein supplementation in this disease, at least in communities where malnutrition is not common. It may well be that in impoverished communities, protein deficiency could have an important bearing on the development and progress of the disease. None the less, anti-tuberculosis chemotherapy alone can produce good results in patients who are undernourished. In toxic patients the liquid protein concentrate has been most helpful in producing stimulation of appetite with consequent gain in weight, and a feeling of well-being. There seems a rational indication for the administration of extra protein in such circumstances, and it would appear reasonable to adopt similar measures in patients who may be losing large quantities of protein in the sputum, pleural fluid or in the urine.

The preparation also proved beneficial in the convalescent tuberculosis patient, particularly when the patient tended to lapse into a state of anorexia, poor appetite and weight loss.

SUMMARY

The composition and qualities required in a protein concentrate for clinical use are discussed and the results of using a new liquid protein extract in several common medical and surgical conditions are described.

We wish to thank the following consultants for specialized reports: Dr. P. M. O'Flanagan, Psychiatrist, Winwick Hospital, Warrington; Dr. I. P. Rowlands, Consultant Physician for Geriatrics, Chester City Hospital; Mr. L. J. Temple, Thoracic Surgeon, Liverpool Regional Hospital Board; and Dr. T. M. Wilson, Physician Superintendent and Chest Physician, Baguley Hospital, Manchester.

We are grateful to Messrs. Bell & Sons Ltd., of Liverpool, who have prepared the liquid protein concentrate 'versitol' and who have afforded us generous supplies for clinical trial.

GENERAL PRACTITIONERS' FORUM

SURGICAL INDUCTION OF LABOUR IN THE HOME

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Specialists deal mainly with uncommon conditions and major procedures, and the vast majority of minor deviations from normality which are dealt with by general practitioners never come within their orbit. Consequently, as most medical literature is written by specialists, a false picture of the over-all pattern of medicine tends to emerge, which can only be modified when sufficient general practitioners publish their experiences in different fields. This article is an attempt to give a true picture of the risks and difficulties associated with the surgical induction of labour in minor deviations from normal pregnancy, and to show that, with careful case selection, surgical induction of labour is a safe and proper procedure for the general practitioner obstetrician to undertake in the patient's home.

Professor Ian Donald (1959) has expressed the opinion that the occasional inert labour following induction, whatever the method, is probably due more to the effects of anxiety and hidden fears on the labour process than to any other factor. Induction is no ordeal to a woman when performed by her family doctor with her own midwife in attendance, and one should consider very seriously whether it is in her best interests to be rushed away to hospital to strangers and to a ritual which may be productive of fear and distress. The woman who has made all necessary arrangements for home confinement is often unhappy at the thought of going into hospital when she has been looking forward to her husband's company and the peace and privacy of her own home for herself and her new-born baby. Her state of mind and personal feelings about the matter cannot be ignored. Careful case selection is essential, however, and the considerations I have mentioned must not allow the obstetrician to retain a woman at home when a home confinement will mean an appreciable increase in the risk to herself or to the fœtus.

SELECTION OF CASES

The following criteria must be satisfied for induction to be considered at home:—

(1) The pregnancy must have advanced to at least 37 weeks and the size of the baby must be in keeping with the dates.

(2) The head must be engaged in a primigravida or must push in easily in a multipara.

(3) The cervix must be 'ripe' and easy to reach with the finger. It is important for the onset of labour to follow soon after induction in the home and this combination is most likely to produce an early onset of labour.

A 'ripe' cervix is soft and easily admits one finger. Cocks (1955), in a study of 133 cases, showed that the average induction-delivery (I-D) interval in cases with an unripe cervix was at least twice that in cases of ripe cervix and that if the os was placed sacrally and was difficult to reach the I-D interval was doubled even in the presence of a ripe cervix.

THE RISKS OF SURGICAL INDUCTION

Cord prolapse.—This should not occur if the head is engaged.

It occurred once in 731 cases in Gibson's series (1952), once in 1,585 cases in Tennent and Black's series (1954), and 22 times in 6,869 cases (0.3 per cent.) in Keettel's series (Keettel *et al.*,1958).

Inert labour.—Psychological factors play a part and inert labour is uncommon after induction in the home.

Prematurity.—This occurs if a poor history has been taken or the size has been estimated incorrectly.

Sepsis.

Placental site retraction.

These last two risks are negligible with an I-D interval of less than forty-eight hours.

The maternal morbidity at Hammersmith Hospital for 1951-56 for vaginal delivery after induction was the same as that after spontaneous labour and the combined stillbirth and neonatal death rate in the induced group was actually lower than the total figure for all deliveries (Cope and Pearson, 1958). At the British Hospital for Mothers and Babies at Woolwich, 4,368 surgical inductions were carried out without a maternal death (Sandys, 1954).

INDICATIONS FOR INDUCTION IN THE HOME

A mild toxæmia occurring in the last few weeks of pregnancy and failing to respond to treatment is the main, and some would say the sole, indication. Careful antenatal supervision, including the follow-up of non-attenders during the last few months, routine weighing and the treatment of any rise of blood pressure above the patient's own normal, or an abnormal weight increase, by diet (salt free, high protein, low carbohydrate), sedation and increased rest, will enable most patients to reach thirty-seven weeks with safety. This has been my experience, with the exception of three cases, two of which were fulminating and required hospital admission before twenty-eight weeks. At thirty-seven weeks or later, if albuminuria has occurred or the diastolic blood pressure has reached 100 mm. of mercury in spite of bed rest and sedation, there is a strong case for induction of labour, provided that induction is likely to be safe and easy. What is to be gained by allowing the pregnancy to continue? The fœtus may grow larger if treatment prevents the toxæmic condition from advancing and labour may start normally, but placental efficiency is deteriorating steadily and the risk to the fœtus is increasing.

Postmaturity is thought to be an indication for induction by the majority of obstetricians but there is still considerable divergence of opinion. The

perinatal mortality in labour ensuing after forty-two weeks of pregnancy is undoubtedly higher than that in the 40th and 41st weeks, but much of this increase appears to be due to mechanical factors causing prolonged or difficult labour. The presence of these factors may tend to delay the onset of labour. There is a strong case for induction of labour at forty-two weeks, however, especially in primigravidæ aged 30 or over, in grand multiparæ and if the pregnancy is not proceeding normally in any way. Many of these cases will not be encountered in domiciliary work but others refuse to go to hospital. A further factor to be considered is a woman's state of physical discomfort after forty-two weeks of pregnancy and the fact that arrangements for the care of herself and the expected baby may possibly break down if pregnancy is further prolonged. Many women rely on their mother, husband or other relative at this time and the person concerned may have difficulty in obtaining leave of absence from work.

Before the induction of labour for postmaturity is considered it is essential that the length of pregnancy should be accurately estimated. If the size of the uterus corresponds with the length of pregnancy at about three and five months, and if fœtal movements are felt by patient or doctor between sixteen and twenty weeks the 'dates' are likely to be correct. Without an assessment before the 20th week an apparent prolongation of the pregnancy may be due to a delayed onset of ovulation (i.e. the woman conceived at a time when her period would have been overdue had it materialized) or the woman may have made a genuine mistake in calculation.

PREPARATION OF THE PATIENT FOR INDUCTION

Once a decision has been made that pregnancy may have to be interrupted, provided that the other criteria are satisfied, the patient is told that an internal examination will be necessary to help in deciding on the best course of action. A gentle vaginal examination is then made and, if the condition of the cervix is satisfactory, the patient is told that it is intended to start her off in labour by breaking the waters. She is told that this will merely involve a similar examination to the one she has just undergone, except that it will last a little longer and during it the bag of waters in which the baby is floating will be broken and some of the fluid will drain away. She is likely to start in labour within a few hours of this and her labour is likely to be shorter than if she had been allowed to go into labour on her own. Unless there is great urgency, arrangements are made with the midwife for the induction to be performed in the patient's home early the next morning and she is told that she is likely to be delivered later the same day.

TECHNIQUE

High or low rupture of the membranes?—The Drew Smythe catheter was introduced at a time when it was thought necessary to preserve the 'bag of waters'. It is now realized that the dangers of a 'dry' spontaneous labour are those of the abnormalities which cause the membranes to rupture prema-

turely and that in a normal presentation and with a normal uterus, loss of amniotic fluid before the onset of uterine contractions, if it alters the course of labour at all, merely tends to expedite its completion. This clinical impression has recently been confirmed in a large series (Bainbridge *et al.*, 1958). Infection can spread from the cervix along the track of the catheter so that a high rupture is no safeguard in this respect. High rupture is much less efficient in initiating labour (the I-D interval was more than double that of low rupture in Bellingham's (1954) series), and may also be dangerous in inexperienced hands, as the fœtal vessels in the placenta may be damaged and the baby may die through exsanguination (Russell *et al.*, 1956). Low rupture of the membranes is therefore the method of choice for general practice.

Low rupture of the membranes.—The patient, who is relieved to know that her baby will soon be delivered, is again reassured that the procedure is not going to be very unpleasant or painful and is told how to operate the gas

Inductions for toxæmia	23
Inductions for postmaturity	3
Total inductions	26
Primigravidæ	8
Multiparæ	18
Induction delivery interval less than 24 hours (in most cases less than 12 hours)	22
Normal delivery	25
Forceps delivery at home	1
Stillbirths	0
Neo-natal deaths	1

TABLE I.—Results of surgical induction in the home.

and air or 'trilene' analgesic apparatus should she require it. In my experience it is rarely needed.

The fœtal heart is auscultated and the patient is placed in the lithotomy position with her buttocks projecting over the side of the bed and is maintained thus by an assistant or by the use of a webbing crutch. After swabbing the vulva with 1 per cent. chlorhexidine solution, two fingers of one hand (the left hand is preferable in a right-handed person) are gently inserted into the cervical canal. Without withdrawing the hand, the blades of a long pair of artery forceps are passed by the other hand along the fingers and the bag of membranes is gripped and torn. Fundal pressure by the midwife may aid in making the bag of membranes more tense. The tearing of the membranes is not always easy as the procedure can be likened to trying to burst a balloon which keeps bobbing away. Some consultants advise a volsellum or toothed forceps for rupturing the membranes but the plain artery forceps are probably safer. The amount of liquor removed initially probably makes no difference to the efficiency of the induction as liquor continues to escape for some time afterwards (Bellingham found that the amount removed made no significant difference). It is essential that there be an adequate break in the membranes, however, and if there is no immediate gush of fluid, the index finger should be put through the hole in the membranes to enlarge it, as recommended by Mayes (1954). Bobbing the fœtal head up and down with the fingers to ensure the escape of further fluid is unnecessary and increases the risk of prolapse of the cord. Stripping the membranes is also unnecessary and a straightforward rupture of the membranes produced an onset of labour within twenty-four hours in 95 per cent. of 6,860 patients in Keettel's series (Keettel *et al.*, 1958). It is wise to *learn* the technique under vision. A Sims' speculum will usually give an adequate view of the cervix.

RESULTS

These are summarized in table I, and details of the last 10 cases are given in

table II. The latent interval between induction and onset of labour was over twenty-four hours in only one case, in which a 26-hour delay in a multipara was followed by a 13-hour labour. There were two cases of primary uterine inertia in primigravidæ, one of which proceeded to normal delivery and the

Case No.	Age	Parity	Length of gestation (weeks)	Indication	Highest B.P. (mm. Hg)	Albumin in urine	I-D interval (hours)	Birth weight of baby (Kg.)
1	33	5	38	Toxæmia	155/100	+	6½	2.81
2	35	4	42	,,	160/100		10½	3.41
3	29	8	42	Postmaturity	—		13	4.37
4	27	3	38	Toxæmia	165/110		5	4.02
5	29	3	39	,,	170/105		9	3.01
6	33	4	36	,,	185/115		12½	2.61
7	29	2	43	Postmaturity	—		5	2.72
8	34	6	39	Toxæmia	150/100	+	39	2.90
9	28	2	39	,,	155/100	+	7	4.08
10	23	1	37	,,	140/100		7	3.20

TABLE II.—Details of last 10 cases of surgical induction in the home.

other to a mid-forceps delivery in the home by a consultant (deep transverse arrest). No cases were undelivered after forty-eight hours. The neo-natal death occurred in hospital after a sudden attack of respiratory embarrass-

Author	Place	Period	Number of cases	Onset of labour within 24 hours (per cent.)	Vaginal delivery within 48 hours (per cent.)
Bushby (quoted by Cope and Pearson, 1958)	Hospital (Hammersmith)	1952–55	517		78
Llewellyn-Jones (1955)	Hospital (Kuala Lumpur)	1953–55	410	over 80	92.8 (with oxytocin)
Clement and Black	Hospital (Lanark)	1950–52	1,585	74.8 (primiparæ) 72.5 (multiparæ)	
Present series	Home	1950–58	26	96	100

TABLE III.—Comparison of results of surgical induction in hospital and at home.

ment in a three-day-old toxæmic baby. Induction was performed in the 40th week and the baby's birth weight was 5 pounds 10 ounces (2.45 kg.).

Case No. 6 started her pregnancy with a blood pressure of 140/90 mm. Hg. At thirty-two weeks it rose to 150/100 mm. Hg, and on two or three occasions at thirty-four weeks and later, 50 mg. of progesterone intramuscularly brought it down again to 140/90 mm. Hg under basic conditions of modified bed rest and sedation. At 36 weeks, while she was on complete bed rest, it suddenly shot up to 185/115 one morning. Progesterone, 125 mg., brought it down to 140/95 mm. Hg that evening, when she was induced. She had previously had large babies and I estimated this one to be at least 5½ pounds (2.38 kg.) and therefore induced earlier than would normally be wise. In retrospect, I could have allowed the pregnancy to progress for several weeks longer with safety if I had used the larger doses of progesterone recommended by Dalton (1957). I did not send the patient into hospital on account of her fear of it and because two younger children would have been seriously affected by her absence.

DISCUSSION

This is a small series, but few general practitioner obstetricians have published their results. Cookson (1954), in an excellent survey of his own results over a period of six years, casually mentions 19 cases of surgical induction for toxæmia and postmaturity with no stillbirths and one unavoidable neonatal death. Condon (1954), after sixteen years' experience, stated that most of his cases came into labour within ten hours of induction, and the longest latent period was nineteen hours. He had no cases of cord prolapse or Cæsarean section.

Any direct comparison with a hospital series is manifestly unfair to the latter, as it will contain a large proportion of cases which have to be induced in spite of an unfavourable condition of the cervix and a smaller proportion which must be induced before thirty-seven weeks. Nevertheless, an explanation must be found for the relative lack of efficiency of surgical induction in hospital as compared with that in the home (see table III).

Part of the discrepancy is explained by the greater use of the less efficient high rupture of the membranes. In Bushby's series, only 75.3 per cent. of those induced by high rupture were delivered vaginally within forty-eight hours, whereas the figure for low rupture was 89.8 per cent. In my opinion, however, a major reason lies in the simple friendly atmosphere of a home induction where anæsthesia is rarely needed, and the procedure in terms of mental strain can be regarded as a minor one. Indeed, it is so simple and straightforward that there is a temptation to perform elective inductions, which must be resisted strongly as coming into the category of meddlesome midwifery. Keettel and his associates end their article describing the good results of 6,860 such inductions with a firm conclusion that elective induction of labour is not recommended.

SUMMARY

Cases of mild toxæmia of pregnancy not responding to treatment, and occasional cases of postmaturity, can safely be induced surgically in the home by low rupture of the membranes.

Criteria are laid down for the selection of cases and a personal series of 25 consecutive cases is discussed.

The technique of induction is described in detail. Anæsthesia is rarely necessary.

If induction is performed in the morning, labour usually ensues within four hours and delivery usually occurs the same day. The ease of induction in the home is felt to be due in part to the friendly atmosphere.

In spite of the ease of induction and speed of delivery in selected cases, elective induction of labour is not recommended.

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'IONEXTEN' DEPOT THERAPY WITH SPECIAL RELATION TO DISEASES OF INVOLUNTARY MUSCULATURE

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The advantages of sustained therapeutic blood levels of certain drugs released slowly from their compounds with ion-exchange resins have been demonstrated by various workers during the last two or three years. Kekwick, for instance, showed that, whilst oral administration of free creatinine resulted in a sharp and high blood level followed by rapid elimination, the 'bonded' creatinine resinate gave a sustained blood level, without peaks, for at least eleven hours. The difference between these new resin-drug compounds and the conventional 'enteric-coated' tablets is that the latter are only *delayed* release tablets, whereas the resin-drug compounds release their drug constantly under the influence of free ions in the digestive juices and so provide true sustained action. All methods involving the use of enteric coating must depend upon variables in the digestive process which will affect the breakdown of the enteric coat; the resin-drug compounds depend only upon the presence of free ions, being so compounded that they release their drugs at a rate giving the required duration of activity.

The 'ionexten' (resin-drug) preparations are designed to give a therapeutic effect for ten to twelve hours so that doses are given only at breakfast time and, if necessary, at bedtime. At the same time, by the avoidance of high concentrations of drugs in the blood stream, there is a reduced incidence and severity of side-effects. This report is concerned with the product 'spastipax' which contains the resin-bonded equivalent of hyoscyamine sulphate 0.35 mg., atropine sulphate 0.05 mg., hyoscine hydrobromide 0.025 mg., and amylobarbitone 65 mg.

RESULTS

Peptic ulceration.—Twelve cases of known peptic ulceration were treated with 'spastipax' in addition to the usual dietary regime, but no alkali. These were proven cases in which x-rays had shown typical duodenal

ulceration (or deformity of the duodenal cap) or gastric ulceration. No placebos were given. Two tablets morning and night were given to each patient, and eight patients stated that the pain was relieved entirely, two stated that the pain was much less and thought that the tablets had helped a great deal, and other symptoms such as waterbrash and 'wind' had completely gone. Two patients did not benefit at all. Seven found they had dryness of the mouth of whom two said it was severe; the other five experienced no side-effects at all. Constipation was found in four cases, and difficulty in focusing the eyes in one.

The treatment was stopped after three weeks, and simple antacid therapy instituted, the pain recurring in seven cases as did other gastric symptoms, but disappearing entirely after resumption of 'spastipax'. After two more weeks on this treatment the dosage was reduced to one tablet morning and night, and the patients are doing well on this maintenance dosage with no side-effects.

Diaphragmatic hernia.—Two patients with this condition were treated with 'spastipax', having failed to respond to treatment with antacid, sedation and pethidine-containing medicines. Both found considerable relief from their symptoms, and the effect on one was dramatic in three days. Both complained of dryness of the mouth, but the substernal pain and postural heartburn disappeared.

Non-specific ulcerative colitis.—Only one patient with this condition was treated. It was of long standing and the patient had had several thorough hospital investigations to exclude any other bowel conditions. This patient was treated with 'spastipax' in large doses, with no response at all. The patient continued to have severe spasmodic pain and diarrhœa. It was the opinion of the consultant surgeon that the patient would come eventually to operative treatment.

Biliary colic.—Three patients were chosen in whom x-ray examination had shown that the gall-bladder was non-functional or poorly functioning; in addition, in two there were calculi in the gall-bladder. All three were having repeated attacks of biliary colic associated with flatulent dyspepsia. One had refused operative therapy and the other two were on the waiting list for surgical treatment. All gained considerable benefit from regular doses of 'spastipax', two tablets morning and night, and relief from all symptoms was immediate. Indeed, the absence of symptoms in one case caused this patient to wonder whether operative treatment was necessary. Slight dryness of the mouth was observed in all three cases.

Dysmenorrhœa.—Six patients with severe and debilitating spasmodic dysmenorrhœa were treated; all had tried numerous remedies, both medical and home. Four gained freedom from the severe pain and were able to carry on with their work, whereas previously the pain caused absence from work. One, though she still had a great deal of pain, remarked that 'the pain is nothing like it was'. One patient gained no relief at all, and the remaining patient did not return after therapy was given. The success of

treatment in this condition appeared to depend upon starting the tablets two days before the period was due to begin, and continuing throughout menstruation. Two tablets morning and night were taken by each patient.

Parkinsonism.—Four cases of Parkinsonism were treated. They showed the usual rigidity of extrapyramidal type with tremor and forward falling gait, were of long standing and hopelessly unable to help themselves. All four were upset by the constant dribbling of saliva. Treatment with drugs such as benzhexol and ethopropazine had given considerable relief so far as the tremor and gait were concerned, but the excessive salivation continued despite their use. Each patient was given 'spastipax', two tablets morning and night, with immediate improvement in the salivation. There is no doubt that in these cases the improvement was dramatic so far as salivation is concerned and it was a pleasure to see how psychologically improved they were after gaining such relief.

Night sweats.—Night sweating associated with tuberculosis was completely eliminated in one patient by the taking of two 'spastipax' tablets at 1700 hours. Another patient who had undergone investigations for profuse sweating at night time, and in whom no pathological condition could be demonstrated, has maintained complete freedom from this condition by taking a single 'spastipax' tablet at night.

Condition	No. of cases	Much improved	Slightly improved	Not improved
Peptic ulceration	12	8	2	2
Diaphragmatic herniation	2	2	—	—
Ulcerative colitis	1	—	—	1
Biliary colic	3	3	—	—
Dysmenorrhœa	6	4	1	1
Parkinsonism (salivation)	4	4	—	—
Night-sweats	2	2	—	—
Total	30	23	3	4

TABLE I.—Results obtained with 'spastipax' tablets in 30 patients.

Side-effects.—Of the total of 12 patients in the series exhibiting side-effects, all complained of dryness of the mouth, severe in two cases; four complained of constipation and one of difficulty in focusing.

DISCUSSION

Although this was not in any sense a controlled clinical trial, the impression gained is that a large proportion of the cases treated gained relief from the 'spastipax' formula: 17 of 24 patients were more or less completely relieved of pain from visceral spasms and three others were improved, whilst its use for decreasing salivation and sweating was successful in all of the six patients to whom it was given for this purpose.

There is not sufficient evidence to show clearly whether the incidence of side-effects was lower than with unbonded drugs, but 60 per cent. of

patients experienced no side-effects at all and probably only 10 per cent. had side-effects of any severity.

There was little doubt that the therapeutic effect of the tablets was considerably prolonged and, although the duration of effect naturally varied from patient to patient, there was never any necessity for more than one dose in twelve hours. Of the great convenience and economy of this form of medication, there is, of course, no doubt, and one was impressed with the consistently reliable effects obtained in all cases which responded to treatment.

SUMMARY

Twenty-four patients with painful visceral spasm of various types, four with excessive salivation due to Parkinson's disease and two with excessive night-sweats were treated with 'spastipax' tablets: at breakfast time and at bedtime.

This twelve-hourly dose of resin-bonded belladonna alkaloids and amylobarbitone proved highly satisfactory in 23 of these 30 patients and provided some relief in three others.

Some side-effects of the belladonna alkaloids were seen, but these were not usually severe, and were more than compensated for by the relief obtained with economy and convenience.

ATYPICAL VIRUS PNEUMONIA

By JOHN STEPHEN, M.B., Ch.B.
Late Captain, Royal Army Medical Corps

With the incidence of classical lobar pneumonia decreasing, and that of atypical pneumonia increasing, the following cases are of interest to the practitioner as they show such a consistent symptomatology. The patients, who were all children in their early teens, were resident in a large army co-educational boarding school in Germany. The cases occurred over the space of one year, and were all admitted originally to the school sick-bay; three were later transferred to the nearest military hospital.

CASE RECORDS

Case 1.—A girl, aged 13 years, was admitted on May 22, 1959, with a temperature of 99.6° F. (37.6° C.) and frontal headache. There were no abnormal physical signs nor did any develop during the next five days. The headache persisted and a fluctuating temperature (99 to 103° F. [37.2 to 39.4° C.]) continued until she was transferred to hospital on May 27. The day before this, a non-productive cough developed. No treatment except aspirin was given. An x-ray of the chest revealed consolidation of the lingular lobe.

Case 2.—A boy, aged 15½ years, was admitted on October 24, 1958, with a persistent frontal headache and a temperature of 103° F. (39.4° C.). The headache improved about twenty-four hours after admission but the pyrexia (between 99.6° and 102.8° F. [37.6° to 39.3° C.]) continued until his transfer to hospital on October 29; prior to this a non-productive cough developed. At no time were there

any abnormal physical signs. Aspirin was given to relieve the headache. An x-ray of the chest revealed left lower lobe pneumonia.

Case 3.—An intelligent spastic boy, aged 14 years, was admitted on March 11, 1959, with influenza. At the time there was an epidemic in the school. For the first few days he improved and then his temperature increased again to 102° F. (38.9° C.). He complained of giddiness, frontal headache and a very troublesome non-productive cough. This continued for a further week with pyrexia fluctuating between 99° and 105° F. (37.2° and 40.6° C.), usually between 100° and 102° F. (37.8° and 38.9° C.), and no change in symptoms. There were no abnormal physical signs except his right-sided spasticity. Aspirin, 10 grains (0.6 g.) six-hourly, was initially given but this was stopped after a few days because of an urticarial rash which was thought to be due to the aspirin. In fact it disappeared as soon as the drug was withheld. He was transferred to hospital on March 2, 1959. An x-ray of the chest revealed consolidation of the axillary segment of the right upper lobe.

Case 4.—A boy, aged 12½ years, was admitted on May 3, 1959, with a temperature of 100° F. (37.8° C.) and a heavy cold and cough. Pyrexia subsided and he was feeling much better until May 5, when he suddenly developed a temperature of 101.2° F. (38.4° C.). There were no abnormal physical signs but his cough became more troublesome. The following morning he developed a frontal headache which continued for some days. On May 7, he was found to have diminished movement at the left base and pyrexia of 102° F. (38.9° C.). A diagnosis of virus pneumonia was made and chlortetracycline, 250 mg. four times a day, was given for seven days. Although no chest x-ray was taken, it was felt that this case was without doubt similar to the other three.

It was interesting to observe that this boy, who had suffered from a punctate psoriasis of both arms and legs for some years, improved considerably during this illness. Previously it had been resistant to most local applications.

DISCUSSION

The paucity of physical signs is well known in this type of pneumonia but it is interesting to note that in all these cases the presenting symptom, and in two cases the only symptom, was frontal headache. A non-productive cough developed some four to five days after the start of the illness. No organism was found in the cases admitted to hospital and the disease was presumed to be viral in origin. All the patients were back at school within three weeks.

TO COUGH OR NOT TO COUGH?

By D. S. NACHSHEN, M.B., B.S.

London, N.W.2

For all practical purposes there are two kinds of cough: the useful and the useless. Likewise there are two kinds of cough remedy: the expectorant and the cough sedative. These should be intelligently used, having first established the cause of the cough by clinical and radiological examination. There seems to be no place in therapeutics for the preparation combining both an expectorant and a cough sedative.

EXPECTORANTS AND COUGH SEDATIVES

An expectorant drug, when taken orally is said to irritate the vagal nerve endings in the stomach thus reflexly stimulating bronchial secretion, and

easing the expulsion of less viscid sputum. Ipecacuanha and ammonium chloride are thought to act in this way. There is much doubt as to whether this is, in fact, the mode of action of this type of expectorant but it is the most generally accepted explanation at present (Alstead, 1939; Gordon, 1957). A cough sedative, usually given in the form of a linctus, acts centrally, depressing the response of the 'cough centre' in the medulla to stimuli originating in the respiratory passages. Examples of cough sedatives are morphine, codeine, methadone and pholcodine.

The rational management of cough should serve both to rid the patient of phlegm and to rid him of cough when it serves no useful purpose. The measures available are: (1) The sedation of a useless cough throughout the day and night; (2) encouragement of expectoration by day and sedation of cough by night. Two groups of drugs therefore need to be used separately in the correct management of cough. The duration of activity of both expectorants and cough sedatives given in pharmacopœial doses does not exceed a few hours. It is as pointless to give an expectorant at bedtime as it is to give a linctus to facilitate the morning 'session' of expulsion of sputum so common in bronchitics.

PHARMACOLOGICAL IRRATIONALITY

Perusal of the *British National Formulary* and of a catalogue of 'ethical' proprietaries shows that there is a number of readily available preparations which combine in each dose both expectorant and cough sedative drugs. This irrational marriage has persisted in the 1957 edition of the B.N.F. in the formulæ for ipecacuanha and morphine mixture B.P.C. and for ammonium chloride and morphine mixture B.P.C., and for nine frequently prescribed 'ethical' proprietary medicines. Non-ethical 'patent' medicines are even more guilty in this respect. It is said in favour of preparations containing both types of drug that they 'promote expectoration and relieve irritating cough'. It is difficult to believe that they do, in fact, achieve both these objectives simultaneously.

In addition to the pharmacological irrationality of using such proprietary medicines the cost of average dosage is about a third higher than using a simple expectorant by day and a linctus at night when calculated as total cost to the National Health Service. The average cost of a day's treatment (four doses each of 4 ml.) with the nine proprietary medicines studied is 6.8 pence. Treatment of a productive cough with two doses, each of 15 ml., of a most effective expectorant, compound sodium chloride mixture B.N.F. in hot water during the day, with one dose (4 ml.) of methadone linctus (the most expensive B.N.F. linctus) at night costs 5.1 pence per day. The cost of three doses each of 15 ml. of ammonium chloride and morphine mixture and ipecacuanha and morphine mixture B.N.F. is 3.6 and 3.9 pence respectively. In spite of their comparatively low cost, however, their pharmacological rationale appears to be non-existent. It is hoped that they will be excluded from the next edition of the *British National Formulary*. It seems

inadvisable to prescribe cheaper medicine merely for economy, particularly if the effects of its ingredients are directly antagonistic to each other.

Preparations containing bronchodilators such as ephedrine and theophylline derivatives have been excluded from this study as these drugs are neither true expectorants nor true cough sedatives.

SUMMARY

It is both uneconomical and therapeutically illogical to treat cough with preparations containing both an expectorant and a cough sedative.

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JACK THE BABOON

The Epilogue

By R. N. WOODSEND, M.B., B.S.
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In my short note on 'Jack the Baboon' (*The Practitioner*, 1959, **182**, 748), I concluded by saying: 'I never heard more, but have often wondered what became of him'. I have not had long to wait. As a result of the publicity which the article received in the South African newspapers, I am now able to complete the tale. For the information I am indebted to *The Natal Daily News*, through Dr. C. Pijper of Merebank, Natal.

Jack was caught at a farm near Pretoria when he was very young. He grew up as a great pet of the family and when his owner joined the 3rd South African Infantry he took him along and he was adopted as mascot and taken on the regimental strength. He saw active service in both Egypt and France and was wounded twice. It was on account of the second wound that he came under my care.

In May, 1921, this wound became inflamed and blood poisoning set in, and the poor fellow died on May 23, 1921. By special permission of the municipality he was buried on his owner's farm, and a regimental tombstone was placed over his grave.

JOHN CAIUS

THE VERSATILE DOCTOR

By IRENE LISTER

DR. CAIUS, whose unique mace was exhibited with many other Cambridge treasures at Goldsmith's Hall earlier this year, presented this plain cylindrical rod of gilded silver, with its head supported by four scaly serpents, to the college he refounded four hundred years ago, known affectionately to generations of medical students as 'Caius'.

EARLY DAYS

Dr. Caius (fig. 1), born John Key or Kaye in Norwich in 1510, was a man of many talents: President of the Royal College of Physicians of London nine times, writer of books of wide interests, humanist and man of culture, and physician to most of the Tudor rulers. He yet found time to lecture on anatomy for twenty years.

As a young student Key had come to Cambridge and taken up residence at Gonville Hall to which was attached a hostel named Physwick's or Physick's Hostel. Gonville Hall was mostly for students of medicine, but John Key studied divinity, doing many translations from Greek and Latin, and becoming first a Fellow and then the Principal of Physwick's. At 29 he left England and became professor of Greek at Padua. A man's natural talents usually come to the fore, however, and soon John Key became attracted to medicine, studying under John Baptist Montanus, and qualifying as M.D. He then lived for eight months in the house of Vesalius, studying anatomy from that great master. By now Key had latinized his name to Joannes or Johannes Caius, although he is usually referred to as John Caius. After his studies in practical work were done he travelled throughout Italy to study in the libraries where the manuscripts of such doctors as Galen were treasured. A tour of France and Germany followed, but it is probable that he lectured also, for when he returned to England in 1544 he was quite a well-to-do man.

THE ANATOMIST

Knowledge of anatomy had sunk to a low level here, and John Caius reintroduced its study. Although he had returned to Cambridge and started in practice, at the personal request of Henry VIII he started the delivery of lectures to the surgeons in London besides being appointed the king's physician. He was a fellow of the Royal College of Physicians in 1547, the year of Henry's death.

For a time he practised in Shrewsbury, where he wrote a treatise on the sweating sickness, a form of plague that recurred frequently, especially in East Anglia: this contains keen clinical observations on the treatment of

the complaint. He then went to Norwich, and finally back to Cambridge where he settled for the rest of his life, except for his visits to London.

During this time he had been appointed physician to Edward VI, and then to Mary Tudor, and it was she and her husband Phillip who gave him the royal license to refound his old college Gonville Hall, then sunk to a parlous state. The doctor endowed it with his personal fortune, and when its Master

FIG. 1.—An engraving from a painting of Dr. Caius.

died two years later, in 1559, Dr. Caius was persuaded to become the Head of his Foundation. Under his wise tutelage the college flourished, being known then as it still is today as Gonville and Caius College. Many eminent men received their training there in his time, and subsequently many famous doctors have been associated with 'Caius', including William Harvey.

In Caius' time anatomy was one of the special subjects provided for study, and one of the Master's privileges was a grant from the Crown to allow him to have the bodies of two condemned criminals yearly for dissection. When a lecture on anatomy was due to be held, a note was sent round to Christ's College, where an eager and clever doctor named Mede resided, and he would come gratefully to sit at the demonstration given by Dr. Caius, so rare was the opportunity to watch a dissection. After the remains of the malefactors were finished with, Caius insisted that a service should be held over their remains in the University Church, and his students had to be present. At a time when human life was sometimes looked on but lightly,

one feels with respect that here was a man of humanitarian principles, as indeed Dr. Caius was.

THE THREE GATES

To refound a college was all very well, but there was much practical work to be done, for Gonville Hall had been in a very decayed state. Dr. Caius purchased surrounding land and built extra courts, allowing plenty of air,

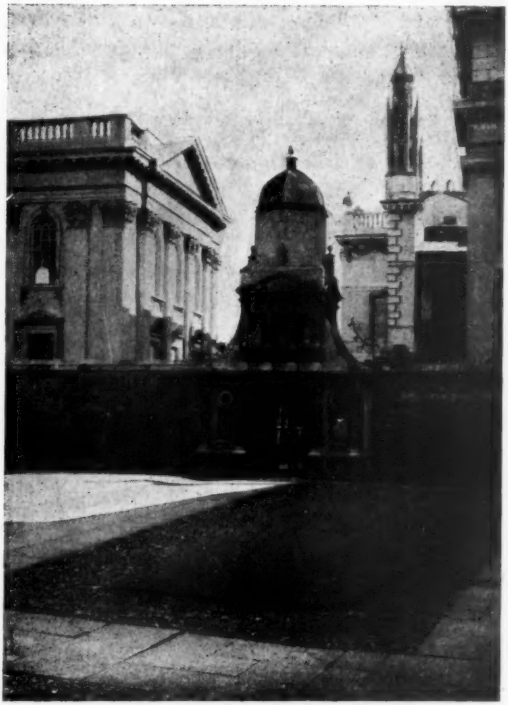

FIG. 2.—The Gate of Honour, Gonville and Caius College, Cambridge. The Senate House in background, and also a pinnacle of King's College Chapel.

a thing not previously thought much of. He also had the unique idea in Cambridge design—and so it remains today—of having a plain entrance gate 'The Gate of Humility', whereas all other colleges have a proud and imposing front gate. To indicate to the student the necessity of entering the college humbly and studying with purity of purpose, there is a second gate into middle court called 'The Gate of Virtue'. Finally the last gate, through which the scholar passed and still passes through to the Senate House to receive his degree was designated 'The Gate of Honour' (fig. 2). This is a famous piece of work and lately in the news when it was decided that the stonework must be repaired. Two of the craftsmen chosen for this delicate

work were elderly men in the 70's and 80's, and one feels this would probably have delighted the founder.

Such was the symbolism of Caius, a typical Elizabethan way of thinking, for by this time Elizabeth I was on the throne of England, and Dr. Caius had been appointed her physician also.

By now he was President of the College of Physicians, lecturer in Cambridge and London, and a busy writer on all manner of things, including a classic study of dogs for the help of his great friend, the naturalist Conrad Gesner.

THE LATTER DAYS

The last days of his life were somewhat saddened by the charge of Romanism directed against him, although he had earlier been accused of being an atheist. It appears he had retained in his college certain books and vestments used previously in Mary Tudor's time, and a report went out from the Vice-Chancellor of the University that he had searched the college and found 'muche popishe trumpery'. Caius resigned his Mastership and prepared for death. He ordered his vault to be got ready in the chapel of the college that he loved and meantime, as he could not eat, he had a series of wet-nurses, and the story runs that according to these women's dispositions, so had the doctor varying moods, which were blamed on to the nurses. Being advised to take milk of a good-natured patient woman, so did Caius become 'beyond the common temper of his age'.

He was buried with honour after his death in 1773 in the burial place he had planned himself in the chapel and over it was placed a most curious monument in the form of a sarcophagus of alabaster. The whole was removed in 1637 when the chapel was enlarged and the erection placed high on the wall. Later still an interesting old document written by a man named Warren in 1719 tells how workmen were 'beautifying' the chapel and accidentally broke a hole into Caius' vault. The narrator tells how he peered into the coffin with the aid of a candle fixed in a long cleft stick. There he saw the remains of the body, yellowish black and fleshy, which yielded to the touch of his stick. He could perceive a long grey beard which —macabre picture—he moved from side to side with his stick, remarking quaintly that the beard had lost all manner of elasticity. (Caius had then been dead about 145 years.) 'The sight', relates Warren, 'occasioned in me serious reflections'.

'MASTER DOCTOR CAIUS'

Dr. Caius' name is immortalized, not only in his college, but in the French doctor in 'The Merry Wives of Windsor', Master Doctor Caius, and it is quite evident from the character's remarks, that Shakespeare was familiar with the work of this famous physician.

CURRENT THERAPEUTICS

CXLIII.—ORAL ANTICOAGULANTS

By M. TOOHEY, M.D., M.R.C.P.
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DESPITE a few contrary opinions anticoagulant therapy is now widely accepted as being of considerable value in the treatment of many thromboembolic disorders. There are probably several reasons why anticoagulant therapy originally aroused such conflicting opinions. First, anticoagulant treatment in most instances treats complications of the underlying disease and does little if anything to 'cure'. For instance, anticoagulants are most widely used in the treatment of atherosclerotic heart disease (coronary thrombosis) to prevent further thrombotic episodes; they can, however, do little to change the progressive nature of the underlying atherosclerotic process. Inevitably therefore the ultimate outlook for a patient depends upon how severely the arteries are affected by atherosclerosis. Secondly, in severe advanced atherosclerosis anticoagulants are usually only of temporary benefit; on the other hand, in cases of mild, isolated atherosclerotic lesions giving rise to thrombotic episodes, with or without anticoagulants the patients may not have further thrombotic episodes for many years, if at all.

Unless the selection of patients is rigidly controlled, these wide variations in the natural history of the disease are bound to give rise to conflicting reports about the efficacy of anticoagulants. The recent controlled trial by the Medical Research Council (1959) showed that long-term anticoagulant therapy reduced the recurrence of coronary thrombosis by as much as 80 per cent. in men aged 40 to 55 and by as much as 50 per cent. in men between 56 and 69.

A third probable reason for the differences of opinion on anticoagulant therapy is that the all-important control of the treatment required to provide adequate therapy at all times is not always effectively provided. It does not appear to be sufficiently appreciated that anticoagulant therapy is effective only so long as an adequate therapeutic 'prothrombin level' is maintained. To maintain adequate anticoagulant therapy continuously over weeks and, more particularly, over months and years, is by no means an easy matter and requires considerable clinical skill in the administration of the anticoagulant drugs combined with expert laboratory control.

INDICATIONS

Anticoagulant therapy has now been widely used for the treatment of coronary thrombosis for many years and is accepted by most authorities as being of considerable value in reducing the mortality rate especially in

severe attacks. More recently, long-term anticoagulant therapy has been used for the prevention of further attacks of coronary thrombosis (Medical Research Council, 1959; Owren, 1954; Toohey, 1958c). Whilst it is still too early to give an absolutely conclusive assessment of the value of such long-term anticoagulant therapy for the prevention of coronary thrombosis, there appears to be sufficient evidence to warrant adoption of this treatment in most patients.

Anticoagulant therapy has achieved striking success in reducing the occurrence of embolism in patients with rheumatic heart disease. Considerable success has also been achieved in reducing the mortality rate from pulmonary embolism following operations and deep venous thrombosis.

In recent times attention has been focused on the use of anticoagulants in the prevention of further attacks of cerebral thrombosis. Good results have been reported in reducing the occurrence of focal ischæmic attacks (Fisher, 1958; Millikan *et al.*, 1955) and in preventing further episodes of cerebral thrombosis (McDevitt, 1958). It is too early to evaluate the results of long-term anticoagulant therapy in cerebrovascular disease but in the treatment of focal ischæmic attacks the use of anticoagulants certainly appears to be justified.

CONTRAINDICATIONS

There are very few contraindications to the use of well-controlled anticoagulant therapy although in some conditions special care and skill may be needed to maintain adequate therapy and to avoid the risk of hæmorrhage. For the treatment of an acute thrombo-embolic illness, especially when the patient is being treated in hospital under constant supervision, anticoagulant treatment is rarely contraindicated except in patients with bleeding diathesis, subacute bacterial endocarditis and perhaps in malignant hypertension because of the risk of cerebral hæmorrhage. Patients with severe liver or renal disease will require smaller than average doses of the anticoagulant drug. Patients with peptic ulcers will need special care to avoid too great a rise in the prothrombin time, but with such care anticoagulant therapy is not necessarily contraindicated. Similarly, extreme caution is necessary in treating patients in the later months of pregnancy.

AVAILABLE ORAL ANTICOAGULANTS

Since the discovery of the first oral anticoagulant, dicoumarol, by Karl Link in 1941 (Link and Campbell, 1941), many new oral anticoagulants have been discovered and have come into clinical use. Oral anticoagulants can be divided into two groups: the coumarin compounds and the indanedione derivatives. All these drugs act in a similar fashion by reducing the concentration of factor VII (proconvertin), prothrombin and factor IX in the blood, thereby producing a prolonged 'prothrombin time' ('prothrombin time' is used here to mean the coagulation time as measured by either Quick's one-stage method or Owren's prothrombin-proconvertin technique (Owren and Aas, 1951)).

Coumarin compounds.—The coumarin compounds in clinical use at present include the following drugs:—

Dicoumarol
Ethyl biscoumacetate ('tromexan')
Phenylpropylhydroxycoumarin ('marcoumar')
Cyclocoumarol ('cumopyran')
Nicoumalone ('sinthrome')
Warfarin sodium ('marevan')

Indanedione derivatives.—These include:—

Phenindione ('dindevan')
Diphenadione
Anisindione ('miradon')

Both coumarin and indanedione compounds can be divided into two distinct groups according to their speed of effective action, i.e. rapid acting and slow acting. After an initial loading dose the rapid-acting drugs exert their maximum effect in about thirty-six hours and the effect of this initial dose is usually completely over in a further thirty-six to forty-eight hours.

The *rapid-acting anticoagulants* include phenindione, anisindione, nicoumalone and warfarin sodium. The maximum effect of all these drugs occurs approximately thirty-six hours after the initial loading dose, and practically all the effect has passed off, with the prothrombin time back to normal limits, about forty-eight hours after cessation of treatment. Ethyl biscoumacetate is the most rapid-acting of all oral anticoagulants, and the prothombin time has usually returned to normal approximately eighteen hours or even less after stopping treatment.

The *slow-acting anticoagulants* include dicoumarol, diphenadione, phenylpropylhydroxycoumarin and cyclocoumarol. The maximum effect of these drugs may not develop for forty-eight to seventy-two hours after the initial loading dose and the effect may last for many days. The effect of a single loading dose of phenylpropylhydroxycoumarin, the longest acting of the anticoagulant drugs, may last for as long as five to seven days.

In treating a patient with an acute thrombo-embolic illness it is important not only to bring the patient under adequate cover as quickly as possible but also to be able to maintain adequate anticoagulant therapy at all times as easily as possible. Because of their slow and prolonged cumulative action, which may take days to appear, the slow-acting oral anticoagulants are undoubtedly more difficult to control than the quick-acting drugs, especially for the treatment of acute thrombo-embolic illness. The quicker-acting drugs have the advantage that any change in the maintenance dose is quickly reflected in the prothrombin estimation. Therefore, because any change in dose or sign of incorrect dosage is rapidly reflected in the blood estimation, the quick-acting drugs are far easier to use and the correct maintenance dose of the anticoagulant is more quickly arrived at.

CHOICE OF DRUG

Now that several satisfactory anticoagulant drugs are available which are easy to control and predictable in their action it is time to discard those anticoagulants which are less easy to control. The effect of ethyl biscoumacetate passes off so rapidly that it is very difficult to maintain effective anticoagulant control in the majority of patients. On the other hand, as mentioned earlier, the prolonged cumulative effect of the slower-acting anticoagulants, such as cyclocoumarol, diphenadione, phenylpropylhydroxycoumarin and dicoumarol, makes these drugs also less easy to control, particularly if the daily maintenance dose has to be changed from time to time owing to changes in the patient's health, alterations in his diet or the simultaneous administration of other drugs, such as oral broad-spectrum antibiotics.

Phenindione has now been in clinical use for a long period and has proved to be a very easy drug to control. The instances of skin rashes (less than 1 per cent. of cases treated) and of agranulocytosis and diarrhœa are so rare as to be of little clinical significance. Phenindione, however, has a drawback when it is used for the treatment of patients on long-term anticoagulant therapy over a period of years (as opposed to its use for the treatment of an acute illness). Over a period of years the required daily maintenance dose of the anticoagulant is bound to vary slightly with changes in the patient's health or diet, or during intercurrent infections (although it is surprising how stable are the requirements of the majority of patients with regard to dosage of the anticoagulant drug). In order to maintain adequate anticoagulant therapy, while avoiding the need to ask the patient to attend for blood tests every week despite the possibility of slight variations in the maintenance dose from time to time, it is important that the anticoagulant drug should have a sufficiently cumulative action to avoid too sharp a fall in the prothrombin time, with the consequent danger of further thromboembolic episodes. For the majority of patients, once the daily maintenance dose has been correctly assessed, phenindione is a very satisfactory drug for use in long-term as well as short-term therapy. For a minority of patients, however, in whom the required maintenance dose may vary slightly from time to time for some reason not always apparent, the cumulative effect of phenindione is not sufficient to provide adequate cover when the patient is attending for blood tests at intervals of four to eight weeks or even longer.

Warfarin sodium has a rapidity of action similar to that of phenindione, is extremely easy to control and has a very predictable action. The only toxic side-effect noted has been alopecia in rare instances. Because of its quick and predictable action, it is as easy to control the treatment of an acute thrombo-embolic illness with warfarin sodium as with phenindione; in addition, however, warfarin sodium has a slightly more sustained effect, which makes it more suitable for long-term therapy in the majority of patients. Considerable experience has now been obtained in the use of this

drug and it is probable that, with its rapidity of action, predictability of response and slightly more sustained effect than phenindione, in conjunction with the fact that it causes no serious side-effects, it is the best single anticoagulant available for both short-term and long-term therapy. Moreover, warfarin sodium is the only oral anticoagulant which can be administered by other routes, such as intravenously, intramuscularly and rectally. There is little to be gained therefore by the introduction of new anticoagulants of a similar nature, such as anisindione, as they are unlikely to have very different characteristics from drugs which are already available and which therefore have the advantage of having been subjected to considerable clinical trial and assessment of the correct initial, and average maintenance, doses needed.

DOSAGE

With all oral anticoagulant drugs an initial loading dose is necessary to produce the desired effect on the prothrombin level. It should be clearly understood that, within certain limits, increasing the amount of the initial loading dose will hasten the effective action of the drug, thereby bringing the patient under adequate anticoagulant cover more rapidly. If, however, too big an initial dose is given a pronounced cumulative effect will develop, lasting many days, with the undesirable eventual result of too great a rise in the prothrombin time. The excessive cumulative effect of too big an initial dose will also upset all further calculations as to the subsequent daily maintenance dose needed to maintain adequate anticoagulant cover. In the long run therefore, giving too big an initial loading dose only increases the time required to assess the exact daily maintenance dose and thereby makes anticoagulant control more difficult. If it is considered essential to bring the patient under adequate anticoagulant cover as rapidly as possible this should not be achieved by giving larger initial loading doses or by using very rapid-acting oral anticoagulants, such as ethyl biscoumacetate, which are too erratic to maintain adequate therapy easily over weeks or months; instead, heparin should be given for twenty-four to thirty-six hours until the full effect of the oral anticoagulant has been achieved.

Initial dosage.—With phenindione the initial loading dose should not exceed 300 mg. The maximum initial dose of warfarin sodium should never be more than 50 mg., with an average of 40 mg. (Toohey, 1958a). With all oral anticoagulants it is important not to give a second dose until the maximum effect of the initial dose has been achieved. With warfarin sodium, phenindione, nicoumalone and anisindione this is in about thirty-six hours in the majority of patients. A convenient practice is to do the first prothrombin estimation on the morning of the third day of treatment, which will in most instances be about thirty-six hours after the initial dose. By this time (if too big an initial dose has been avoided) the maximum effect of the initial dose will have developed in the majority of patients and the first maintenance dose can then be given.

Maintenance dosage.—With phenindione the average maintenance dose is

usually 100 mg. a day, with the majority of patients falling in the range of 50 to 150 mg. For warfarin sodium the average daily maintenance dose is 8 to 9 mg. with a variation of 5 to 15 mg. in the majority of patients.

LABORATORY CONTROL

The basic essential for adequate laboratory control is a reliable thromboplastin. Any variation in the potency of the thromboplastin extract, either from day to day or between different batches, makes anticoagulant control much more difficult. A reliable thromboplastin preparation should not vary more than one second from day to day for normal controls using Quick's one-stage technique. The advantage of Quick's technique is its simplicity. Owren's method, however, although more complicated and time-consuming, is also more sensitive and so reflects any change in the dosage of the anticoagulant drug more quickly than Quick's technique. Therefore in the early stages of anticoagulant therapy, before the exact maintenance dose has been arrived at and also at other times when there may be a variation in the maintenance requirements, it is easier and quicker to adjust and maintain the anticoagulant requirements with Owren's method than with Quick's technique (Toohey, 1958b). For long-term therapy also, Owren's method appears to give slightly better results than Quick's in maintaining adequate anticoagulant control.

PERIODS OF DANGER DURING ANTICOAGULANT THERAPY

As soon as the exact maintenance dose has been determined it is perfectly feasible to allow the majority of patients on long-term anticoagulant therapy to have routine blood tests only once every six to eight weeks and still to maintain adequate control. With such infrequent blood tests, however, it is essential for both the patient and the doctor to be constantly aware that in certain circumstances the patient may get out of control, with consequent danger. Intercurrent infections, especially when in addition the patient is not eating and if broad-spectrum antibiotics are being given, may cause a marked rise in the prothrombin time unless the maintenance dose is reduced. So also may the onset of heart failure, any change in the usual diet, and the administration of certain drugs, such as large doses of aspirin or phenylbutazone. All these eventualities may make it necessary to change the dose of anticoagulant if control is not to be lost. It is thus essential to warn the patient that in the event of intercurrent infections, changes in the diet or any deterioration in his general health, extra blood tests will be necessary, and that he should not wait for the next routine appointment.

HÆMORRHAGE DURING ANTICOAGULANT THERAPY

In my opinion the danger of hæmorrhage has been exaggerated. The occurrence of minor hæmorrhage, such as slight epistaxis, is not uncommon when adequate anticoagulant therapy has been given. Such minor episodes do not call for cessation of treatment but merely a regulation of the anti-

coagulant when necessary. Vitamin K_1 should be given only when absolutely necessary as it can rapidly throw the patient out of control. Slight hæmorrhage accompanied by a pronounced rise in the prothrombin time may be corrected by the administration of small doses of vitamin K_1: e.g. 2 to 3 mg. repeated after twelve hours if necessary. Such small doses of vitamin K_1 will not throw the patient out of adequate anticoagulant control. If severe hæmorrhage has occurred larger doses of vitamin K_1 will be necessary: e.g. 10 to 20 mg. Larger doses than this are rarely needed and only make the patient refractory to further anticoagulant therapy.

USE OF OTHER DRUGS WITH ANTICOAGULANTS

Certain drugs enhance the effect of anticoagulants. Broad-spectrum oral antibiotics, such as the tetracyclines, should be given with care when used with anticoagulants, and a reduction in the maintenance dose of the anticoagulant will almost certainly be necessary. Phenylbutazone is known to cause hæmatemesis and should rarely, if ever, be given together with anticoagulants. Similarly, aspirin is well known for its effect on the gastric mucosa and has often caused hæmatemesis and must therefore be avoided. Very large doses of salicylates and quinine, which enhance the effect of anticoagulants, and oily emulsions such as liquid paraffin, which may interfere with the absorption of anticoagulants, should all be avoided.

CONCLUSION

For long-term preventive anticoagulant therapy it is essential, if adequate anticoagulant control is to be maintained at all times, that the patient should be able to cooperate fully in carrying out all aspects of the treatment. If the patient cannot cooperate fully not only will it be extremely difficult to maintain adequate control but the risks of hæmorrhage will be too great to warrant treating such patients.

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PRACTICAL DIETETICS

XI.—FEEDING OLD PEOPLE

By B. R. STANTON

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More and more people are living into their seventies and eighties and even beyond and as food is the biggest single factor in maintaining health and vigour, dietary advice for the elderly is the concern of all general practitioners.

There is no 'special diet' for age just as there is no special age at which a person becomes old. Old folk are individuals but there are certain principles, nutritional and otherwise, which should guide the elderly in their choice of food. Briefly, it may be said that the dietary must be nutritionally adequate, it must be capable of easy mastication and digestion, it must be within their pocket; so far as possible within their established food habits and within their physical powers to buy, prepare and cook.

NUTRITIONAL NEEDS

In order to be nutritionally adequate a diet must contain all the essential nutrients in amounts which meet the individual's needs. A simple way of ensuring this is to see that it contains representatives from the three food groups:—

Building foods

Iron and protein, found in: Fish, eggs and meat—iron especially in liver, kidney and corned beef

Calcium and protein found in: Milk and cheese

Protective foods

Vitamins A and D, found in: Dairy products including butter and margarine, cheese, milk and eggs; fat fish, liver and kidney

Vitamins B complex and vitamin C, found in: Fresh fruit and vegetables, especially citrous fruits, tomatoes and green leafy vegetables

Energy foods

Fats, found in: Dripping, butter, margarine, fat meat and cheese

Carbohydrates, found in: Preserves, sugar, sweets, chocolates, cereals, bread, cakes and potatoes

This arrangement of foods is obviously an over-simplification because bread is not merely an energy food but also contains protein, iron, calcium and vitamins of the B complex. In the average diet bread can contribute as much as a third of the protein required and almost a sixth of vitamin B_1. However, if foods from these groups are included in the day's meals and in the quantities suggested below, there is little likelihood of a deficiency of any essential nutrient.

FOODS AND QUANTITIES

Ideally the dietary should contain a pint of *milk* daily but the quantity should not fall below ½ pint (285 ml.). Condensed or evaporated milk is

suitable although skimmed milk, much of which is sold as sweetened condensed, is lacking in vitamins A and D.

There should be daily at least two, and preferably three, good servings of *animal protein foods*, i.e. fish (fresh or canned) or cheese, eggs or meat—including bacon, ham, canned meats, offal or poultry. Liver or kidney or corned beef should be eaten at least once a week.

Potatoes, freshly cooked—that is, not 'left overs' fried up—should be eaten daily, and *green vegetables* three or four times and an *orange* or a *tomato* twice or three times weekly.

These foods look after proteins and, to a large extent, the vitamins and minerals. Vegetables and fruit also contain roughage which helps to prevent constipation.

Energy foods are the easiest and cheapest to obtain and it is rare to find people eating too few calories. Bread, butter and margarine, sugar, jams and other preserves are all comparatively cheap foods and when eaten to appetite provide sufficient calories. Often the danger is too many rather than too few calories which results in obesity, and when obese patients have to be helped dietetically to reduce their weights it is well to advise first the exclusion of empty calorie foods, i.e. foods which provide only energy, such as sugar, preserves, sweets, chocolates, cakes and biscuits.

MASTICATION AND DIGESTION

Some old people suffer from indigestion, the cause of which is blamed first on one food and then on another until their choice of food is so restricted that it is impossible to obtain a balanced diet. The indigestion may be caused by inability to chew: the patient may have too few teeth, no teeth or a National Health set which is taken out at mealtimes. In these cases food should be minced or mashed and often a smooth sauce or gravy helps to moisten it and make it slip down easily. Meat, minced and mixed with gravy or sauce, need not always be of the same kind nor need it be tasteless. For example, veal may be cooked with a little bacon or ham for flavouring; lamb or beef cooked with onions and other vegetables; chicken or calves' liver can be braised with onions or herbs, minced and mixed with white or brown sauce, as appropriate. Fish may be removed from the bone after cooking and mashed with a white or lemon sauce; eggs may be scrambled and for flavouring mixed with minced ham, cooked bacon or cheese. Cheese may be finely grated and served either raw or in a white sauce. Vegetables should be cooked until soft and then chopped with a sharp knife or mashed well with milk and a little butter or margarine. Fruits may be eaten stewed or squeezed to extract the juice.

Old people need reassuring that their indigestion may be due only to their inability to chew and that if food is mechanically chewed first, by mincing, sieving or chopping, then it can be eaten with impunity. Choice of food is then enlarged and the nutritive value of their meals improved.

Some elderly people cannot digest fat easily and it is wise to avoid fatty

dishes, i.e. fried foods, rich pastries and cakes, fat meats such as pork and duck, and rich sauces. On the other hand, many old people *can* tolerate fried foods and it is commonly held that scurvy is prevented in some old men because of the vitamin C obtained in fried potatoes, bought at the local fish and chip shop.

COST OF FOOD

Old people living on retirement pensions often have to choose between buying food or the little comforts and luxuries which by habit have become necessities. Hunger can be stayed with buns and cups of tea but 'hidden hunger', that is bodily need for food, can only be met by the more expensive protein and protective foods. Of the cheap sources of animal protein, cod, haddock and fish roes are as good nutritionally as the more expensive plaice or sole. Herrings and kippers are cheap but not always a good buy for those whose eyesight is poor and who cannot see the small bones. Tough and hence cheaper cuts of meat, suitable for braising and stewing, are equally good as roasting and grilling joints. Stews are easy to prepare and they have the added advantage that they can be cooked, vegetables and meat together, in one pot on a single gas ring.

Cheese is one of the cheapest animal protein foods but is regarded, falsely at times, as being indigestible This reputation may be due to the fact that it is not properly masticated or that it is over-cooked. When cheese is toasted or grilled until the protein is tough and stringy it is likely to cause symptoms of indigestion, but grated cheese or soft curd cheeses, are usually well tolerated.

Generally, the made-up or prepared protein foods, for example pies, sausages, fish cakes and canned meats, are more expensive foods and of less food value (per unit of cost) than fresh meat or fish.

Fruit and vegetables are expensive and fruit especially is often regarded as a luxury. For people living alone there is some difficulty in buying vegetables in economic quantities. Even a small cauliflower, cabbage or swede is too large and will wilt or shrivel before it can be used; on the other hand, carrots and onions, which store easily, are poor sources of vitamin C. For those living alone a daily orange or large tomato will provide sufficient vitamin C and for most of the year these fruits are fairly cheap.

FOOD PREPARATION

Buying, preparation and cooking of food are all chores which become more difficult as activity wanes. Arthritis, heart disease, and inability to go out in bad weather all make it difficult to obtain supplies and to prepare food. Men usually fare worse than women because most of the elderly men are widowers who are unused to cooking. They tend to eat prepared or packaged goods (bread, biscuits, cakes, preserves) which for the most part are lacking in animal protein and vitamin C. For them, if these can be afforded, canned meats and other canned goods are useful and some firms are now putting up stews, vegetables, fruits, milk and milk puddings in small packs of one

or two portions. The Canned Foods Advisory Bureau, 37 Baker Street, London, W.1, has some useful information on canned goods in a leaflet entitled 'Small packs for old folk'.

'Meals on Wheels' or similar meal services, which provide a cooked mid-day meal at low cost, are very helpful for the elderly. Inquiries at the Women's Voluntary Services, the local authority centre or local Red Cross headquarters usually reveal a welfare service of this kind.

It must not be forgotten that uncooked meals can be as nourishing as cooked ones: a piece of cheese, a raw tomato, bread and butter and a glass of milk constitute as good a meal, nutritionally, as any exotic meal a famous chef can devise.

SPECIMEN MENU

Breakfast:	Cereal with milk and sugar, and/or egg, bacon, smoked haddock, sausage, fish roe Bread and butter or margarine Marmalade—optional Beverage
Mid-morning:	Beverage, biscuits or bread and butter (optional)
Mid-day:	Stewed or braised lamb, mutton, stewing steak, chops, liver or other offal *or* cold meat (fresh or canned), *or* roast meat, *or* steamed, grilled or fried fish Potatoes Vegetables or salad Pudding and/or cheese and bread or biscuits, *or* raw or stewed fruit Beverage
Tea:	Bread and butter Tomato or jam or other preserve Cake (optional) Beverage
Supper or High Tea:	(in the latter case omit tea and take a drink or snack at bed-time) Cheese *or* egg *or* fish *or* cold meat Bread and butter or margarine Tomato *or* pickles *or* salad Fruit *or* cake *or* pudding Beverage
Bed time:	Drink and a sandwich or biscuit

FOOD HABITS

Bad food habits, made worse by ill health or lack of teeth, are difficult to break. At the end of life it is usually better to modify the bad rather than to attempt a revolution, which may upset the patient emotionally and improve neither his health nor his food habits. Some old people will not eat vegetables but they can be persuaded to take orange or other citrous fruit juice, sweetened and diluted (it is important, in order to conserve vitamin C, that this juice be freshly prepared from whole fruit). Some will not drink milk but may be persuaded to eat milk pudding or to drink milk soup. Some refuse red meat but may be encouraged to eat eggs, cheese or white meats. It is a question of spending time to find out which foods are accept-

able and then ensuring that each group, referred to previously, is adequately represented. When food habits are so bad as to preclude the possibility of choosing a balanced diet, then explanations must be given and the patient must be strongly urged to improve and widen his choice.

Timing of meals.—The timing of meals is important: old people should have small meals, spread over the day, and start with a good breakfast—a cup of tea is not enough. At bedtime a snack may help to induce sleep, although a drink is not always a good thing because fluid at bed time may mean broken rest with trots down a cold corridor to the lavatory.

During convalescence.—In most instances old people who are temporarily off their normal food through illness should be encouraged to keep up the protein and vitamin C content of their diet by taking milk and eggs. One pint of milk (570 ml.) is equivalent in protein value to approximately 3 ounces (85 g.) of cooked meat, and one egg (7 g. protein) equals about 1¼ ounces (35 g.) of cooked meat.

Fruit juice or strained tomato juice provides vitamin C and helps to give a clean fresh feeling to the mouth. Carbohydrate can be given as sugar in drinks, as cereals with milk or as bread and milk. Meat soups or meat extracts are of little value in themselves but will sometimes encourage appetite for more nourishing foods.

REVISION CORNER

PRACTICAL ASPECTS OF EMERGENCY BLOOD GROUPING

THE underlying principles of blood grouping tests are comparatively simple. On the surface of the red blood cells are a number of different blood group substances or *agglutinogens;* in the plasma or serum are one or more *agglutinins* or *antibodies*. A serum containing an anti-A agglutinin, when mixed with cells bearing the agglutinogen A, will react specifically with those cells in such a way that they are attracted together to form clumps or agglutinates. Cells which do not carry the agglutinogen A are unaffected and remain evenly distributed. Similarly, sera containing other agglutinins such as anti-B or anti-D will react specifically with cells bearing their corresponding agglutinogens. Although nine separate blood group systems, each of which has a number of subgroups, are recognized, only the ABO and Rh(D) groups are of clinical importance in the majority of cases.

In the compatibility (or direct matching) test we wish to know whether the *patient's serum* contains any agglutinin against the blood group substances on the *donor cells* which will cause them to be clumped and destroyed. Since the agglutinins in the patient's serum are probably nothing like so strong as those in the grouping serum (which has been obtained from selected donors) the observed reactions may be very much weaker than those seen in the grouping tests.

NO PLOY FOR THE AMATEUR

But blood grouping is no ploy for the amateur. Gone are the days when it was regarded as a simple test, performed in a few minutes, and requiring little apparatus. The most practical advice which can now be given to a practitioner is that he should do his utmost to avoid having to undertake emergency grouping and matching of blood for transfusion. Since the setting up of the National Blood Transfusion Service there is probably nowhere in the British Isles where the doctor will be completely cut off from advice and help should he require it.

Where there is any chance of removing the patient by road or air to a hospital it may be possible to tide him over the journey by giving plasma or dextran. It should be noted, in passing, that dextran in the blood stream is apt to cause rouleaux formation of the red cells which may confuse subsequent grouping and matching tests. The hospital's job will be made easier therefore if they receive, with the patient, a 5 to 10 ml. sample of clotted venous blood removed before starting the dextran infusion.

In remote areas, by a bit of forethought, it may be possible to arrange with a competent laboratory that blood samples from as many as possible of the population are grouped in anticipation of an emergency so that a 'walking blood bank' is formed. This precaution will save time but it does not obviate the necessity for direct matching tests between the patient's and the donor's bloods before transfusion is undertaken.

No doctor should knowingly depart to a wilderness where he may have sole responsibility for an emergency transfusion without first gaining some practical experience in the requisite techniques. Most Transfusion Centres and Blood Banks will be found to be very willing to discuss the methods and apparatus most applicable to the particular locality and can probably arrange a short course of tuition.

Such technical details as are given here are only suitable for use by the unprepared doctor who has been unexpectedly cut off from civilization, who has practically no reagents or apparatus at hand, and who is faced with a patient who will shortly die if no blood is given. They are certainly not methods recommended for routine use and if carelessly performed the tests may give a false sense of security.

REAGENTS REQUIRED

Grouping sera.—To determine the ABO and Rh groups of the patient and his potential donors the doctor will need a stock of anti-A, anti-B and anti-Rh(D) sera. If possible the anti-Rh(D) serum should be one which is known to react well with the slide technique; this is an important point to note because sera can vary considerably in strength and speed of reaction when different methods are employed. Any 'instructions for use' issued with the grouping serum should be carefully followed—short-cuts and modifications may give false results. Fluid sera should be stored in a freezing cabinet; dried sera may be stored at room temperature. The potency of the

serum may decline with storage so the expiry date should be verified.

Blood samples.—(1) *The patient.*—The patient's red cells will be required for grouping tests and his serum for the matching test.

About 2 to 10 ml. of venous blood is taken into a sterile container and allowed to clot. When the clot has retracted the serum is removed for the matching test; cells can then be obtained by poking a wooden applicator stick into the clot and transferring about five drops to a test tube containing 1 ml. of normal saline.

(2) *The donor.*—A donor of the same ABO and Rh group as the patient should be chosen and therefore his cells only will be needed. Five drops of blood should be taken into 1 ml. of normal saline by pricking the donor's ear lobe or finger.

Apparatus.—The grouping and compatibility tests are best done on glass slides which permit a microscopic reading of doubtful results. The slides should be clearly labelled with the name of the person being grouped and with the type of antiserum being used. Contamination of one serum by another or by red cells or vice versa will spoil the tests. After use with one serum the Pasteur pipette should be rinsed three times in tap water and in normal saline before the next serum is taken up and this rinsing is repeated each time a move is to be made to a different serum or cell suspension.

ABO GROUPING

Label one microscope slide for each person who is to be grouped. One drop of anti-A serum is placed towards the left end of each slide and one drop of anti-B nearer the other end. One drop of patient's or donor's cell suspension is added to each drop of serum on one slide and is mixed by gentle rocking and rotation of the slide. When a potent grouping serum is used agglutinates about the size of grains of red pepper may begin to appear within half-a-minute but where no clumping is visible, even when viewed against a white background, the gentle rocking of the slide must be continued for not less than five minutes before one can state with confidence that no reaction is occurring. A microscopic check of the naked-eye appearance is advisable to confirm a negative result.

Cells agglutinated by anti-A but not by anti-B belong to group A.

Cells not agglutinated by anti-A but agglutinated by anti-B belong to group B.

Cells agglutinated by anti-A and anti-B belong to group AB.

Cells not agglutinated by anti-A or by anti-B belong to group O.

RH GROUPING

One drop of anti-D serum which is known to be suitable for the slide test is placed on a glass slide and to it is added an equal drop of a thickish cell suspension or a drop of whole blood. After thorough mixing with the clean end of an applicator stick the slide is held over an opal glass electric light bulb and is gently rocked and rotated. The light provides the necessary warmth for the test and makes the reading easier. A good serum will agglutinate D Rh-positive cells within a minute or two but apparently negative results should be scrutinized for five minutes after which time the effects of evaporation may begin to confuse the appearance.

ABO AND RH GROUPING BY ELDON CARDS

These cards, prepared by the Nordisk Insulinlaboratorium in Denmark, are useful for the person who has to group blood occasionally in an emergency without the usual equipment.

On the surface of each card a drop of anti-A, anti-B and anti-D grouping serum has been dried. A drop of water is used to reconstitute each serum and a carefully measured drop of whole blood obtained by ear-prick is well mixed with each serum. Some practice may be required before the exact quantities and the necessary speed of operation are achieved. The card is tilted back and forth for three minutes and then examined for the presence of agglutinates. Any departure from Eldon's prescribed technique will increase the risk of false reactions and during long or improper storage of the cards the sera may become inactive—a point which may not be recognized at the time of use.

THE COMPATIBILITY OR DIRECT MATCHING TEST

A test of compatibility between the patient's serum and the donor's cells must be done every time a bottle of blood is to be transfused even though donor and recipient are thought to be of the same ABO and Rh group. The reasons for this are that (1) technical or clerical errors may lead to a false report of the blood group and (2) the patient's serum may contain an antibody which will destroy the donor's cells.

To make transfusion completely safe a series of elaborate and time-consuming tests are absolutely necessary. The more such tests are simplified and speeded up the greater is the danger that incompatibility will go undetected. The doctor must, perforce, choose the least risky and most informative technique possible with the equipment and time available to him but this should not be taken to mean that a simple test will be so worthless that it can be omitted.

The following method will detect ABO incompatibility but will disclose few antibodies against other groups. If the patient is one who might be classed as a 'dangerous recipient' the test will do little to safeguard him from a possibly incompatible transfusion.

Two drops of the *patient's serum* are placed with two drops of the *donor's cell suspension* in a small test tube and are thoroughly mixed. If a centrifuge is available the tube should be spun rapidly for three minutes, after which the cells are transferred by Pasteur pipette to a glass slide and a microscopic search made for agglutinates which would indicate incompatibility. If no centrifuge is available the contents of the test tube will require longer for their interaction at room temperature—at least ten minutes and preferably thirty minutes should be allowed before the results are read. If no tubes are available the drops can be mixed on a glass slide which should be placed in a Petri dish containing moist cotton-wool to prevent evaporation during the thirty minutes before the microscopic reading. Even if the clumps consist of only 4 or 5 cells the bloods must be regarded as incompatible and a further donor matched.

It may happen that no donor is found of the same group as the patient and so group O blood may have to be given to a patient of group A, B or AB. Since the group O donor's plasma may contain strong anti-A or anti-B agglutinins or hæmolysins which may destroy the recipient's cells a 'minor matching test' in which the *patient's cells* are mixed with *donor's serum* should be included in the tests of compatibility.

Information on the methods of blood grouping and compatibility testing which are less risky can be found in: the Medical Research Council Memorandum No. 36 'The Determination of the ABO and Rh(D) Blood Groups for Transfusion' (H.M. Stationery Office, 1958); 'A Guide to Blood Transfusion' by R. J. Walsh and H. K.

Ward (Australian Red Cross Society Blood Transfusion Service, Sydney, 1957); and 'Techniques in Blood Grouping' by I. Dunsford and C. C. Bowley (Oliver and Boyd, 1955).

JEAN GRANT, M.B., F.R.C.P.ED.
Director, Regional Transfusion Centre, Oxford.

INDICATIONS FOR OXYGEN THERAPY

OXYGEN is essential for human life, and there is no substitute for it. So, if there is significant oxygen lack, and giving oxygen will relieve it, then oxygen therapy is indicated.

EFFECTS OF HYPOXIA

It would be most convenient to set out a clear-cut list of the signs and symptoms by which oxygen lack could be recognized; but this is impossible because the effects of oxygen are so widespread in the body and its lack is so readily mimicked by an upset in the amounts of other widespread materials such as sugar, carbon dioxide and electrolytes. The effects of severe hypoxia are obvious: in the brain by the presence initially of irrational behaviour, going on to loss of consciousness, and then irreparable brain damage; in the lungs, by the development of pulmonary œdema from capillary damage; in the heart, by irregularities of rhythm going on to anoxic cardiac arrest; and by biochemical changes in the kidneys, liver and all other organs. All these effects, however, are non-specific, and when the hypoxia is of less striking degree it is commonly unrecognized. Talkativeness, restlessness, pulmonary hypertension, and so on, which often arise from oxygen lack, are easily misdiagnosed. Thus, minor, but most important, deficiencies of oxygen are often uncorrected by oxygen therapy, even when they can be, simply because they go unrecognized.

Cyanosis is generally taken to be the best indication of hypoxia, but this has its difficulties apart from the well-known errors from peripheral rather than central cyanosis. Since it is the absolute amount of reduced hæmoglobin, rather than the proportion of reduced to oxygenated hæmoglobin, which determines cyanosis, anæmic subjects will not readily get central cyanosis even though their oxygen lack is extreme, whilst polycythæmic subjects readily go blue at high levels of oxygen saturation. Even apart from this error, however, and the possibility of cyanosis from other pigments, such as methæmoglobinuria, the difficulty about using central cyanosis as the sign of hypoxia is that it cannot be recognized by most observers until the saturation is less than about 80 per cent., by which time the blood oxygen tension (which is what matters to the patient) is reduced to almost half the normal because of the S-shape of the oxygen dissociation curve. Thus, it is prudent to remember the errors in recognizing hypoxia by cyanosis, and to regard its presence as usually meaning not just hypoxia, but gross hypoxia.

In summary, cyanosis generally means severe hypoxia, and less severe degrees of hypoxia have to be recognized by such non-specific indications

as restlessness, and even by signs such as a raised jugular venous pressure (in cases of respiratory failure) which are generally associated with other factors in the minds of most clinicians.

RESPIRATORY FAILURE

In practice, the most common indication for giving oxygen in a medical condition is for an *acute bronchiolitis or broncho-pneumonia complicating emphysema and chronic bronchitis*. The condition is recognized by the patient's copious and purulent sputum, high fever, distressed breathing (usually with some accompanying wheeze and scattered râles in the chest), warm hands, and cyanosed lips. The jugular venous pressure is often raised, which indicates cor pulmonale complicating the condition; the veins in the eye fundi are often engorged and limb twitching is often observed, if this is felt for by lightly clasping the patient's outstretched hands. Yet, obvious as the condition appears, its differential diagnosis may be difficult from acute left-sided heart failure (say, hypertensive or following myocardial infarction), or even from a primary neurological condition (such as a cerebrovascular accident) if the combination of hypoxia and carbon dioxide retention in such cases of emphysema is severe enough to cause restlessness going on to coma, with papillœdema as well as venous engorgement in the eye fundi. In all these cases of respiratory failure oxygen is urgently needed and it should be given promptly, together with antibiotics, and bronchodilator drugs in the form of either compound spray of adrenaline and atropine B.P.C., or this, together with 10 ml. of aminophylline intravenously. The spray must be given with a nebulizer that produces a suitably fine spray, such as a Collison inhaler or Wright nebulizer marketed by Aerosol Products Ltd. The nebulizer serves the double purpose of relieving the patient's wheeze and wetting the oxygen.

When oxygen is given effectively to such patients it may cause respiratory depression and hence a further rise in the already excessive quantity of carbon dioxide in their arterial blood. This can lead to drowsiness or even coma ('carbon dioxide narcosis'). Fear of the latter has led to the use of intermittent oxygen or even to withholding oxygen altogether. This is quite illogical and a serious misinterpretation of therapeutic endeavour—rather like withholding insulin in severe diabetic ketosis for fear of producing hypoglycæmia! The correct procedure is always to give the oxygen, but to stimulate breathing should the patient's ventilation become seriously depressed, and drowsiness or coma arise as a result of giving the oxygen. It is as well to be sure that the drowsiness is the result of the oxygen by stopping it, in order to be sure of the diagnosis of carbon dioxide narcosis, if the preferable procedure of estimating the arterial carbon dioxide tension is impracticable. If the patient is more alert, but cyanosed, off oxygen, but pink and drowsy with it, then oxygen is continued but ventilation stimulated by giving an injection of nikethamide or amiphenazole. These analeptic drugs are first given in the usual dosage, say, 1 or 2 ml. of niketha-

mide, when the patient usually wakes up dramatically. But the injection may have to be repeated frequently (up to half-hourly) or larger doses may be required. Trial and error, gradually increasing the dose (up to 5 or even 10 ml. of nikethamide), must be used to find the required dose. Such measures may well be life-saving and the oxygen together with the stimulation of ventilation, if needed, will alone often reverse the process of cor pulmonale, which is all too often lethal. All such patients are medical emergencies and oxygen is urgently indicated for them. A few require tracheostomy as well as the oxygen and other measures, but their management is a special problem outside the scope of this article.

Pneumonia.—Oxygen is similarly needed by many patients with pneumonia who have no pre-existing emphysema, but in them the problem of carbon dioxide retention as the result of oxygen therapy will not arise.

Asphyxia.—Oxygen is needed whenever asphyxia is occurring from insufficient air getting to the lungs, because of mechanical obstruction. Obviously the obstruction itself is first removed if practicable, but when it occurs from mediastinal tumours, status asthmaticus, and the like, this cannot immediately be done, so that one important item, amongst other treatment, is to enrich what air can be got into the lungs by oxygen. In fact, in any condition in which artificial ventilation is needed oxygen is indicated for that ventilation if it happens to be to hand. One practical example of its urgent requirement, is in cases of cardiac arrest during diagnostic procedures in hospitals. This unfortunate complication should always be considered a possibility, and facilities and skill should always be available for prompt artificial ventilation with oxygen and immediate cardiac massage, through a chest incision, once the diagnosis of cardiac arrest is made in such circumstances. Oxygenation and cardiac massage must be done within approximately three minutes if irreparable brain damage from anoxia is to be avoided.

Carbon monoxide poisoning.—Tissue asphyxia may be a consequence of diminished oxygen carrying power of the blood resulting from carbon monoxide poisoning (or such conditions as very severe anæmia). There is no interference with the passage of air into the lungs or with the transference of oxygen across the alveolar membrane, but the amount carried to the tissues is grossly reduced. Oxygen promptly, and in high concentrations is required (preferably with 5 per cent. carbon dioxide added in the case of carbon monoxide poisoning). The higher the oxygen tension in the blood, the more quickly is the carbon monoxide eliminated. Any extra CO_2 may assist in liberating oxygen from the hæmoglobin and in liberating the carbon monoxide.

CIRCULATORY DEFECTS

In *heart failure*, which is *not* secondary to lung failure, the oxygen saturation is seldom much below 85 or 90 per cent. even though pulmonary œdema is present. Thus, cyanosis is rare, and in general the main treatment is with digitalis, diuretics and other cardiac remedies. In the majority of cases

there is no need to consider oxygen therapy. Nevertheless, it may be helpful because of the marked increase in oxygen tension, even though there is only a small increase in saturation, in the arterial blood when oxygen is given to such a patient even if he has normal lungs. For the same reason it should be considered in cases of *hæmorrhage and shock*.

P. HUGH-JONES, M.D., F.R.C.P.
Lecturer in Medicine, Postgraduate Medical School of London.

NOTES AND QUERIES

Influenza, 1959-60

QUERY.—I am the medical officer to a factory employing some 1,200 work people. I have been asked about the possibility of active immunization against influenza during the coming season, and before taking up the matter of mass inoculation, I wondered if it was possible to find out from an epidemiologist the likelihood, or otherwise, of there being a major epidemic within the next twelve months. If you could discover this for me I should be greatly obliged.

REPLY.—We have had extensive outbreaks of Asian (A2) influenza in the last two winters and of influenza B early this year. There should be a fairly high immunity among the population to both viruses. There are at present no indications leading us to expect a major outbreak in 1959-60. On the whole it seems likely that there will be less than during the last two years. Several pharmaceutical firms have influenza vaccines on the market and the best of these, preferably given in November or early December, in a single dose, may be expected to reduce incidence by about two-thirds.

C. H. ANDREWES, M.D., F.R.C.P., F.R.S.

Influenza Vaccine

QUERY.—I intend giving influenza vaccine this autumn, so I should be glad of any information relating to the appropriate vaccine to be used, as there are so many on the market that it is difficult to judge the one which is considered to be of the greatest value.

REPLY.—Clinical influenza of viral origin is caused by one or other of the two main influenza viruses A and B. Since it is difficult to predict which of these two viruses is likely to be mainly responsible for the winter outbreaks of influenza in any particular year, a vaccine containing both type A and B viruses should be used. Furthermore, since these viruses may show antigenic changes fairly often, the vaccine should contain the currently prevalent variants. The influenza virus vaccines used in the controlled trials sponsored by the Medical Research Council and the Ministry of Health were made at the Wright-Fleming Institute and marketed by Parke, Davis and Company. These vaccines, which are grown on chick embryo tissue, formalin-killed and absorbed on low concentrations of aluminium phosphate, are unlikely to cause much local or systemic reaction, but inquiry should be made to ensure that the recipient is not sensitive to egg. The dose is 1.0 ml. given in November or December.

PROFESSOR ROBERT CRUICKSHANK, M.D., F.R.C.P. D.P.H.

Diphtheria-Pertussis Immunization

QUERY (from a reader in Eire).—A child who has come under my care had, I believe, two injections of combined anti-diphtheria/pertussis vaccine but has not had the third. The second injection was given eighteen months to two years ago. Would it do to give him only the third injection now, or shall I have to give him the ordinary course of three injections?

REPLY.—One further dose of 1 ml. of anti-diphtheria/pertussis vaccine should suffice in this instance. The reasons for this suggestion are as follows:—

(1) The two previous doses of diphtheria prophylactic will have been sufficient to establish a satisfactory basic immunity and the further injection after an interval of eighteen months to two years is ideal.

(2) The child has not had whooping-cough since the first treatment and is now past the dangerous period during the first two years of life. One further dose of prophylactic should be a satisfactory stimulus.

W. POWELL PHILLIPS, O.B.E., M.R.C.S., L.R.C.P., D.P.H.

Poliomyelitis Immunization

QUERY.—When a child has been given a 1-ml. dose of poliomyelitis vaccine and has not attended for the second dose for over seven months, I have given two doses with an interval

of three to four weeks between. Do you consider such cases should have further reinforcing doses in another seven or eight months, or do you consider this course would give the same protection as the normal procedure?

REPLY.—Recent evidence suggests that the antibody titres obtained after vaccination depend principally upon the total amount of antigen given. The need for multiple doses is simply a reflection of the difficulty of giving enough antigen in one or two doses to ensure an adequate response in 100% of individuals inoculated. A fourth or fifth dose of Salk vaccine in the United States has been advocated because of the failure to achieve adequate immunization with fewer injections using their average commercial vaccines. On the other hand, British vaccines appear to be 'three-dose' vaccines rather than 'four-dose' vaccines.

In the course of injections given in this case the response is not likely to be greatly different from three doses spaced otherwise. Provided that the vaccines previously used have been of high potency these three injections would be a perfectly adequate course.

ALAN P. GOFFE, M.B.

Male-Pattern Alopecia

QUERY.—I am often asked if there is anything that can be done for falling hair and premature baldness in young men. Could you tell me if there is any treatment of benefit in the absence of obvious disease?

REPLY.—Premature baldness in young men is termed male-pattern alopecia and is a forerunner of the normal senile alopecia. Genetic predisposition is important. It is inherited as a male dominant but may also occur in women as a recessive gene. The family history is therefore all-important in prognosis. Castrates do not lose their hair so that androgens seem mainly responsible, but ageing itself is a factor which also increases the baldness.

Seborrhœa (also materially influenced by androgenic endocrines) with greasiness of the scalp, dandruff or evidence of seborrhœic dermatitis, often accompanies the male pattern thinning, but is not inevitably present. It would seem that when present in excess the rate of hair loss is increased and the final development of the full senile pattern more quickly attained.

It has been said that there is no effective treatment for premature baldness—'the millstones of inherited genetic patterns, hormonal variation and ageing grind on inexorably to a bare scalp'—but where the seborrhœic state is present treatment designed to control this may well slow up the progress of the alopecia. Such management requires control of the excesses which increase seborrhœa: excessive eating and obesity, excessive drinking, working too hard or at high pressure, not enough sleep with persistent late hours and personal conditions causing stress and anxiety. Many of these individuals are overactive, often obsessional compulsive persons usually chronically fatigued in later years, who set themselves a high standard difficult to maintain with increasing age. This seems very common in women who exhibit this pattern at the menopause possibly related to adrenal androgenic influences.

Massage probably does not help and may indeed cause additional traumatic-massage alopecia when practised too enthusiastically. Detergent shampoos or selenium-containing preparations may control the local signs of seborrhœa as will the routine scalp lotions, e.g. lotion of salicylic acid and mercuric chloride B.P.C. Explanation of the probable mechanism of hair loss as being part of the virile state in men, and with some indication of the prognosis (especially in women, that they are not likely to lose all their hair) is essential for proper treatment. It seems important also to recommend some form of local treatment if only to relieve anxiety and because the patient expects it: the use of scalp lotions and ultra-violet light has its place in this respect.

GEOFFREY HODGSON, M.B.E., T.D., D.M.

Pharyngeal Hæmorrhage and Influenza

QUERY (from a reader in Iraq).—During two epidemics of influenza in our country in the summer of 1957 and the winter of 1958, I noticed in more than 60% of the cases I examined a submucous hæmorrhage in the back of the pharynx. I tried to find such patches of hæmorrhage in other diseases of the nasopharynx such as simple common cold or acute pharyngitis; I even searched among cases of laryngitis (other than 'flu) or bronchitis and I could not find this sign.

Will you kindly let me know the significance of this sign as regards diagnosis of influenza from the clinical point of view?

REPLY.—Hæmorrhages in the palate or pharynx have not been previously reported in any number of patients during recent epidemics of Asian type of influenza, although epistaxis was common in children. Pharyngeal hæmorrhages, however, have been noted not infrequently in virus cases of adenoinfection, both in this country and in America. I saw submucous hæmorrhages on the palate in 1939 during a mixed influenza A and B epidemic at a Naval Hospital. No adenovirus antigen was, of course, available at this time but it is very likely that

some of the cases were in fact caused by adenovirus infection because of the frequency of this group of viruses in acute respiratory disease in Servicemen. In view of the fact that more than 60% of cases of influenza in the epidemics referred to in the question showed this physical sign it may be asked whether there was any abnormal state of the capillaries in the patients quite apart from influenza. For instance were any of the cases on the verge of vitamin C deficiency or had they received heavy dosage with aspirin and so forth? It would certainly be incorrect to use evidence of submucous hæmorrhages in the throat in the differential diagnosis of influenza virus infection.

C. H. STUART-HARRIS, M.D., F.R.C.P.

Portable Electrocardiographs

QUERY.—I shall be grateful for information about portable electrocardiographs which are not too complicated to work, but are easy to carry about.

REPLY.—If a general practitioner contemplates buying an electrocardiograph he must necessarily be prepared to make himself proficient in its use and interpretation. The situation is illustrated by the absence, so far as I know, of practical postgraduate courses designed to this end. The technique of recording an electrocardiogram is quickly learned but there are pitfalls which would take too long to describe here. Interpretation requires long and intensive study not only of tracings but of cardiology as a whole. Misinterpretation of electrocardiograms has resulted in much unnecessary invalidism. In general practice time is probably better spent in taking an accurate history and in making a thorough examination. Moreover, the National Health Service provides for electrocardiograms where necessary, through hospitals and the domiciliary consultant service.

There are several good portable instruments on the market. For general practice the instrument should be easily portable and powered by a battery if isolated areas are to be visited. The advantages of a direct-writer are self-evident but there is something to be said for a photographic type since interpretation is not then expected at the bedside.

Among firms who deal with electrocardiographs the following may be mentioned in alphabetical order:—

Cambridge Instrument Co. Ltd., 13 Grosvenor Place, London, S.W.1.

Exal, 13-17 Pennant Mews, Kensington, London, W.8.

Philips Electrical Ltd., 45 Nightingale Lane, Balham, London, S.W.12.

Siemens Edison Swan Ltd., Electromedical Section, 155 Charing Cross Road, London, W.C.2.

Sierex Ltd., 241 Tottenham Court Road, London, W.1.

from whom further particulars may be obtained.

C. J. GAVEY, M.D., F.R.C.P.

Thalassæmia

QUERY (from a reader in India).—What is the pathology and surest diagnostic sign or measure of thalassæmia? What is the latest treatment and/or management? What is the prognosis in a boy of 7 years suffering from the disease for the last three years?

REPLY.—Thalassæmia is an inherited abnormality of hæmoglobin production. The hæmoglobin variant affected is the normal adult pigment called hæmoglobin A. If the gene for thalassæmia has been inherited in a single dose (heterozygous thalassæmia minor) the suppression of hæmoglobin A production is usually slight and can be compensated by an increase in the number of red cells, but if additional strain is experienced, such as infection, pregnancy, or hæmorrhage, the condition may become severe. If the gene for thalassæmia is inherited in the double dose (homozygous thalassæmia major), the disorder is always serious and often not compatible with reaching adult age. As the basic difficulty is that of forming hæmoglobin A the hæmatological picture resembles that of the hypochromic anæmia of iron deficiency but, unlike that deficiency anæmia, thalassæmia does not respond to iron therapy. One of the surest diagnostic signs is a combination of normal or even high serum iron level with a hypochromic blood picture.

Thalassæmia only affects the formation of hæmoglobin A. Thus other hæmoglobins continue to be formed and may be present in increased amounts. For instance, a sickle-cell trait carrier who is heterozygous for the genes responsible for hæmoglobin A and for hæmoglobin S usually possesses more A than S but if he is also heterozygous for the thalassæmia gene, hæmoglobin S will be prevalent and he will be suffering from a modified sickle-cell anæmia (sickle-cell thalassæmia, microdrepanocytic disease). In thalassæmia certain normal hæmoglobins, hæmoglobin F (fœtal) and hæmoglobin A_2 which either disappear in early infancy or are present only in very small amount, will persist into a later age and form a larger than normal proportion of the total hæmoglobin.

The management of thalassæmia requires protection from stress so that the expanded bone marrow is allowed to compensate so far as possible by producing an increased number of the hypochromic red cells. Transfusion should

only be given in emergencies because, as there is no iron deficiency, repeated transfusions may cause hæmosiderosis. For the same reason iron treatment is not only unnecessary but can be positively dangerous. With continuous care homozygotes can sometimes be nursed through infancy and adolescence and once adult age is reached the prognosis becomes more favourable, but patients can never aspire to a fully normal life.

H. LEHMANN, M.D., SC.D., M.R.C.P., F.R.I.C.

A Holiday in Brittany

DR. I. MCD. G. STEWART writes:—I have read with much interest Dr. Douthwaite's two notes on the advisability of T.A.B. inoculation before going to France on holiday. My experience is in line with his. Within a period of six weeks in the early autumn I saw two patients who had just returned from holiday in France. Neither had been inoculated. One proved to have contracted typhoid fever, and the other paratyphoid fever, while on holiday.

PRACTICAL NOTES

Treatment of Pruritus

'AT present, steroids, which are often both effective and well tolerated, supersede all other medications used topically to relieve itching', according to M. R. Caro (*Postgraduate Medicine*, September 1959, **26,** 392). The most commonly used is a 0.5% to 1% hydrocortisone ointment. It is pointed out, however, that 'one should not forget that less expensive ointments, such as boric acid, zinc oxide, 5% ichthyol, crude coal tar and Lassar's paste, are often useful in allaying itch, and are much more economical to use in the large quantities that are usually needed'. Ointments containing drugs that may sensitize the skin should never be used: e.g. all the 'caine' local anæsthetics, the sulphonamides, penicillin, and most of the antihistamine drugs.

In discussing systemically administered drugs the author reports that he has found the antihistamine drugs disappointing, except those that may induce sleep, such as diphenhydramine. The tranquillizers have not proved effective in relieving itching. Of the sedatives, phenobarbitone is 'probably as effective as any', but, the author adds, 'of the many hypnotic drugs available I have found chloral hydrate to be the most useful for inducing sleep in itchy patients'. The use of intravenous procaine to relieve itching is 'fraught with danger that should not be ignored'.

Severe Allergic Reactions to Insect Stings

UNRECOGNIZED fatal cases of systemic reaction to insect stings 'may occur with greater frequency than is realized', according to H. L. Mueller (*New England Journal of Medicine*, August 20, 1959, **261,** 374), who therefore considers that all patients who have had such a reaction to bee or wasp stings should receive desensitization treatment. In a study of 84 such patients over a period of eight years, 75% had a family or personal history of other allergy and tended to have more severe reactions than other patients. Cases with only local reaction, to whatever extent, were not included in the series. As multiple sensitivity is usually present, a mixed whole-insect extract of equal parts of bee, wasp, hornet and yellow jacket was used. Treatment was started with the dilution of extract which gave the 'initial positive test', and this ranged from 1:1,000,000,000 to 1:1000. Starting dosage was 0.5 ml., gradually increasing to a maintenance dose of 0.2 to 0.3 ml. of a 1:100 dilution. If testing is not carried out the initial dosage recommended is 0.05 ml. of a 1:1,000,000,000 dilution. Patients were given a maintenance dose every four weeks during the insect seasons and every six weeks throughout the winter, for a period of three years. Of the 76 patients who were treated, 40% had subsequent stings and, with one exception, all who were stung while on a maintenance dose of 0.15 ml. or more of a 1:100 dilution, or who were stung after completing three years' treatment, had no resulting systemic symptoms.

Extradural Hæmorrhage

IN a review of 83 cases of extradural hæmorrhage in Melbourne, Reginald Hooper (*British Journal of Surgery*, July 1959, **47,** 71) expresses the view that 'a mortality-rate of 10% should be regarded as a reasonable figure in centres where neurosurgical facilities exist. A higher rate may have to be accepted in other situations, but at the present time a mortality-rate in excess of 28% indicates a low standard of medical education or a poor organization'. In his own series there were 19 deaths (23%), but a comparison of the mortality-rate in the first and second halves of the period covered by the survey show that in the latter half the rate was only 9% compared with 41% in the first half. This 'very significant fall in mortality-rate' is attributed 'to increased experience, to improvements in the organization in the hospitals concerned, and in very large measure to an increased awareness of the condition amongst house-surgeons and general practitioners'.

In general, extradural hæmorrhage is seen as a complication of blunt head injuries of the closed type. In the author's series, 39% were the result of road traffic accidents, 36% were due to falls, and 16% were due to a blow on the head. The hæmorrhage often follows relatively mild injuries. Thus, of the 27 patients in whom adequate information on this point was available, 14 sustained impacts which were of mild degree, whilst in 10 these were of moderate severity. In the last 34 consecutive patients in the series the origin of the bleeding was arterial in 15, arterial and venous in five, and tears in the dural venous sinuses in eight; in the remainder the origin was not clear. In diagnosis the site of the impact is of the greatest importance. Every recipient of a blow in the temporoparietal region must be suspected as a potential candidate for an extradural hæmorrhage.

Testosterone in Aplastic Anæmia

PROMISING results are reported by N. T. Shahidi and Louis K. Diamond (*A.M.A. Journal of Diseases of Children*, September 1959, **98**, 293) from the use of testosterone in the treatment of aplastic anæmia in children. In the authors' experience 'the treatment of aplastic anæmia in childhood and adolescence has been one of the most hopeless and discouraging problems in the practice of pædiatrics'. Of the 40 cases seen at the Children's Hospital, Boston, in the past twenty years, only two had a spontaneous remission, and only one survived after four years. Corticosteroids alone produced no beneficial effect. They report their findings in five cases. Testosterone was given as testosterone propionate or 'linguets' of methyltestosterone, in a dosage of 1 to 2 mg. per kg. body weight per day. Corticosteroids were also given in the form of triamcinolone, 8 to 12 mg. a day. Remissions occurred in all but one child who died from simultaneous occurrence of gastrointestinal hæmorrhage and overwhelming infection. In an addendum they record the results in five further cases: two showed a good response, one a moderate response, and two died from acute and generalized hæmorrhage two months after treatment was started. Side-effects included acne, flushing of the skin and mild hirsutism, which occurred in all children two or three months after the institution of treatment with testosterone. None of the children showed noticeable spurts of statural growth but 'impressive gain in body musculature and strength was noted, especially in boys'.

Grenz-Rays and Pemphigus

FAMILIAL benign chronic pemphigus is a condition which begins in early adult life, affects both men and women, and runs a chronic course punctuated by remissions and exacerbations. It affects the skin of the flexures, the primary lesion being a small flaccid vesicle. Rupture of the vesicle leads to the formation of denuded, moist, cracked areas, often covered by dried exudate and parakeratotic crusting, and liable to be misdiagnosed as intertrigo. Although probably a developmental condition and therefore incurable, according to I. Sarkany (*British Journal of Dermatology*, July 1959, **71**, 247), 'a reasonable period of control of the disease can be achieved by Grenz-ray therapy which has the advantage that it does not produce serious sequelæ even after repeated administration to the same site'. He reports his findings in six cases, in which this form of therapy was effective for at least six months. The period of follow-up ranged from eight to sixteen months, and the remissions following treatment lasted from four to fourteen months. 'The length of remission', it is stated, was 'consistently greater than that obtained with any other single measure'. A divided-dose scheme gave better results than the single-dose method. Although there did not appear to be much difference between the results obtained by the use of three doses of 200r, or three doses of 300r, at weekly intervals, the latter on occasion proved more effective.

Pneumonia and Rheumatoid Arthritis

EIGHT cases of interstitial pneumonia, pulmonary fibrosis or honeycomb lung associated with rheumatoid arthritis are recorded by Bruce Cruickshank, of the University Department of Pathology, Glasgow Royal Infirmary (*British Journal of Diseases of the Chest*, July 1959, **53**, 226). Although the pathological changes varied somewhat from case to case, there were certain features common to all of them, including the interstitial situation of the significant lesions, the non-specific nature of the inflammation and the fibrosis associated with bronchiolectasis. The cellular elements of the interstitial pneumonia were similar to those which occur in the synovial tissue and other inflammatory lesions of rheumatoid arthritis. In addition, there was a tendency to the formation of definite nodules of such cells, sometimes with germinal follicles. It is suggested that the sequence of events in these cases starts with a non-specific interstitial pneumonia. At this stage the process is reversible and resolution probably occurs in many patients. If the inflammation persists, fibrosis occurs and becomes increasingly prominent. The main clinical features are progressive dyspnœa and cough, often with expectoration and occasionally with

chest pain. Physical signs are neither marked nor specific. The radiological appearances are those of diffuse reticulation, occasionally accompanied by mottling or nodulation. Although, apart from granulomata in one case, none of the lesions in this series can be regarded as specific, it is concluded that the lung lesions are manifestations of rheumatoid arthritis. In this connexion it is pointed out that 'the joint lesions which have for so long been used as the basic criteria for the diagnosis of rheumatoid arthritis are themselves non-specific in the vast majority of patients'. It is also noted that no evidence of pulmonary lesions of this nature was found in the post-mortem records of over 200 cases of ankylosing spondylitis.

Atropine in Mongolism

THE suggestion that children with mongolism are hypersensitive to atropine has been investigated by J. M. Berg and his colleagues (*Lancet*, September 26, 1959, **ii**, 441). A drop of atropine was placed in the right eye of 19 mongols and 20 similarly retarded children without mongolism. An analysis of the results showed that the mongols tended to react more quickly and that the reaction was more sustained. In both respects the difference was statistically significant. In the authors' view 'the possible relation between the low muscle tone, which is a constant feature of mongolism, and atropine sensitivity raises interesting speculation'. As they point out, 'since atropine inhibits acetylcholine, which is concerned with normal stimulation of skeletal muscle, the two phenomena may be related to the same basic metabolic defect in mongolism'. 'If atropine sensitivity can be confirmed by other workers', they suggest, 'it may guide the development of rational therapy'.

Meckel's Diverticulum

As the result of an analysis of the records of 143 patients with Meckel's diverticula operated upon between January 1937 and July 1958, T. N. P. Johns and his colleagues (*Annals of Surgery*, August 1959, **150**, 241) 'suggest that in many instances an apparently normal diverticulum may be responsible for symptoms'. The series consisted of 71 males and 72 females, 39 of whom were aged 12 years or less. In 121 patients the diverticulum was found as a result of a deliberate search during operation for suspected intra-abdominal disease, and was not diseased. In 89 of these patients it was found at operation for suspected appendicitis. In five cases a diverticulum was found in a hernia sac: twice in an inguinal hernia, twice in a femoral hernia and once in an umbilical hernia. In one of the cases of inguinal hernia it was strangulated; in the others it was normal. In 100 cases (70% of the whole series), the indication for operation leading to the discovery of the diverticulum was appendicitis. In 11 of these patients complications of the diverticulum were present, the appendix being normal in nine and chronically inflamed in two. In the 89 patients in whom the diverticulum was normal, the appendix was normal in 55 (62%), acutely inflamed in 23 (26%) and chronically inflamed in 11 (12%). There were 55 patients operated upon because of a diagnosis of appendicitis, in whom both appendix and diverticulum were normal. These patients are said to fit into a definite clinical pattern characterized by vague abdominal complaints extending over a period of months or years. In practically all cases symptoms were relieved by removal of the appendix and the diverticulum.

In 22 cases there were complications involving the diverticulum: diverticulitis in eight, intestinal obstruction in seven, intussusception in three, ulceration and hæmorrhage in two, omphalomesenteric fistula in one, and strangulation and hernia in one.

Diethylcarbamazine in Filariasis

'SINGLE doses daily of diethylcarbamazine are as effective as three doses daily against microfilariæ of *W. malayi* and are more convenient', according to L. H. Turner (*Annals of Tropical Medicine and Parasitology*, June 1959, **53**, 180), as a result of his experiences with 70 patients on Penang Island. Diethylcarbamazine (the dihydrogen citrate salt, containing 51% of the base) was used as syrup ('hetrazan') and as tablets ('banocide'). All doses refer to the salt. The syrup, diluted 1:10 with water, was used for the smaller doses, which were dispensed with a 10-ml. pipette graduated to 0.1 ml. Tablets were used for the larger doses. The drug was given at about 09.30 hours each day. There was considerable variation in the effects of the smaller dosages against the microfilariæ. Although as little as 0.25 mg. per kg. daily reduced the microfilaria count by 63% over five days, the effect was considered too slow. Larger doses were more rapidly and more regularly effective. Febrile reaction occurred in all but one of 55 microfilaria carriers when the dosage was high enough to remove microfilariæ from the blood. After the febrile reaction had subsided, large increases in dosage never provoked a recurrence of febrile symptoms. Although all the 69 patients followed up were able to take doses of 9 mg. per kg. without side-effects, there was considerable individual variation in tolerance of higher dosages.

REVIEWS OF BOOKS

Hypertension. Edited by JOHN MOYER, M.D. Philadelphia and London: W. B. Saunders Co., 1959. Pp. xxii and 790. Illustrated. Price 98*s*.

THIS massive volume embodies the proceedings of a symposium on hypertension held at the Hahnemann Medical College, Philadelphia, in December 1958, a conference in which 91 contributors participated, only one of whom was from this country. Naturally, much of the material covered is familiar, particularly the sections on physiology and pathology and those dealing with the course and prognosis. There are, however, many sections which strike a new note—e.g. those on the roles of trace metals, of monoamine oxidase and of humoral agents in etiology. There are chapters on the metabolism of the heart muscle, on the juxta-glomerular cells and on the role of sodium and water in pathogenesis. In the section on pharmacology the actions of the ganglion-blocking agents, of Rauwolfia compounds and of chlorothiazide are fully dealt with. In addition there are chapters dealing with remedies which are little used on this side of the Atlantic, particularly the veratrum alkaloids and hydrallazine. In the sections on treatment the necessity for close supervision of the individual patient and for adjustment of the dose of drug in accordance with the response achieved is abundantly manifest. As a corollary it is interesting to note the emphasis placed by our American colleagues on the long-term management of hypertension on blood-pressure readings as taken by the patient himself in his own home.

This book contains a mass of information regarding hypertension which is not readily accessible elsewhere and it should provide a very useful work of reference. As such it should find a place not only in the larger medical libraries but on the bookshelves in hospitals where members of hospital staffs can have ready access. Browsing through such a book should prove informative to any practitioner of medicine, whether in general or specialist practice, as illustrating the extraordinary amount of meticulous and detailed analysis which has gone to build up our present-day conceptions of the etiology and treatment of this common disorder.

Hypertensive Disease: Diagnosis and Treatment. By SIBLEY W. HOOBLER, M.D. London: Pitman Medical Publishing Co. Ltd., 1959. Pp. x and 353. Price 60*s*.

THIS may be fittingly described as a practical book dealing lucidly with a complex subject and clearly addressed to the practising doctor rather than to the research worker or ultra-specialist. In his approach, the author first breaks down the heterogeneous array of conditions associated with high blood pressure into etiological groups—on the one hand those secondary either to remediable causes (adrenal medullary and cortical tumours; unilateral renal disease: aortic coarctation) or to irremediable lesions (e.g. bilateral kidney disease); and on the other the primary or 'idiopathic' cases which form the great bulk of patients with hypertension. The assessment of prognosis based on search for signs of wear and tear in target organs (heart, brain, retina, kidney) is fully discussed, and should prove a valuable guide to the practitioner. In regard to treatment, to which some two-thirds of the book is devoted, there is first a step-by-step correlation of therapeutic régimes with the indications for treatment in individual groups of patients followed by chapters on the use of various specific drugs. A dozen appendixes give details of various pharmacological tests and therapeutic régimes. The precision with which dosage is related to response is noteworthy, and the emphasis is on close long-term supervision of the patient. The current American practice of gauging progress on the basal blood pressure as recorded at home by the patient himself is strongly emphasized, and in fact the only plate in the book is of a girl demonstrating this technique. There are obvious objections to such a practice: not least, it would appear, being the risk of breeding a 'figure-phobia', but the author's case-records make a good case for its adoption, at least in patients with intelligence enough to perform the rite reliably and stability of character enough to come to no harm!

The book is to be recommended to any doctor who is faced with the problem of treating hypertensive patients, and as such it should enjoy wide popularity.

A Textbook of Surgical Physiology. By R. AINSLIE JAMIESON, M.B., F.R.C.S.ED., and ANDREW W. KAY, M.D., CH.M., F.R.C.S.ED., F.R.F.P.S.G. Edinburgh: E. & S. Livingstone Ltd., 1959. Pp. vii and 623. Figures 186. Price 55*s*.

IT is surely a sign of the times and of the direction that surgery is taking that Professor Illingworth, himself a joint author of the best textbook of surgical pathology published in Britain, should have stimulated the writing of a book on surgical physiology by his two senior lecturers. From such breeding we are justified in

expecting a good deal, and we get it. After four general chapters on healing, radiation, fluid balance and metabolism, the organs and the systems are dealt with in separate chapters. It is a pity, however, that the central nervous system and the female genital tract have not been included because they are the preserves of specialists—in some places many of the other systems have become equally cut off by specialists—and the rest of the book is so admirably suited for the general surgeon.

This is more than an account of physiology, for there is much pathology, surgical lore and practical advice as well, but the emphasis is on the application of physiological principles and knowledge to the practice of surgery. It is primarily intended for the postgraduate student to whom it can be strongly recommended as a useful textbook for preparation for the primary F.R.C.S. examination. Like other books with a physiological bearing it contains statements with which some would quarrel as being out of date, which is unavoidable in times of rapid advance. It is written in plain language and there is seldom any doubt what the authors mean, which will be appreciated by readers whose English is not their first language. A selected list of references follows each chapter and the choice of these has been wide but, whilst many of the classic papers have been included, it is discouraging to find so few references to work done in the last five years.

Cancer. Volume V. Edited by RONALD W. RAVEN, O.B.E., T.D., F.R.C.S. London: Butterworth & Co. (Publishers) Ltd., 1959. Pp. viii and 425. Figures 136. Price 85*s*.

THIS volume is devoted to radiotherapy. After an opening chapter on the 'Historical background of radiation in cancer' a series of seven chapters are concerned with general aspects of the subject, such as physical properties of radiation and dosage, and including a chapter on radio-isotopes. The remainder of the volume covers the subject according to the part of the body being treated. Between them the twenty-one contributors, all but one of whom are from this side of the Atlantic, provide a comprehensive and authoritative review of radiotherapy in all its many aspects.

Tuberculosis and Other Communicable Diseases. Edited by J. ARTHUR MYERS, M.D. Springfield, Illinois: Charles C Thomas; Oxford: Blackwell Scientific Publications Ltd., 1959. Pp. xii and 499. Illustrated. Price £5 10*s*.

THIS is a volume of twenty-six chapters dealing with a wide variety of communicable diseases ranging from tuberculosis to herpes simplex ar cat-scratch fever. The objective is to provide th latest information regarding these infectio diseases under the headings of diagnosis, tre ment, prevention and epidemiology and to e phasize the point that, although marke reduced in prevalence and destructiveness, n has yet been eradicated and that further inte fication of preventive measures is required. the whole, the book fulfils its objective reas ably well, although its wide scope has resu in some of the subjects being rather ske covered. The first (and largest) section is dev to tuberculosis and here it is disturbing to BCG being roundly condemned as a prod of tuberculous conditions such as lupus garis, erythema nodosum, mediastinal ader iridocyclitis and intestinal obstructio vehemence with which it is condemned of overenthusiasm rather than reason a to obscure the author's more rational ob to its employment: namely, its destruction of th value of the tuberculin test as a case-findi procedure. Exception might also be taken to t statement that there is ever-increasing eviden to the effect that most reinfections are e genous rather than exogenous, and Bri readers will not subscribe to the dictum th streptomycin should be administered every thi day. The advocacy of a combination of artifici pneumothorax and chemotherapy as good t ment in those parts of the world where the relatively few or no hospital beds, is open question.

The volume throughout contains much th is of interest to the student of public healt and of preventive medicine but, although w produced, its cost seems out of proportion t value.

Instrumentation in Anesthesiology. By WILLIAM H. L. DORNETTE, M.D., and VERNE L. BRECHNER, M.D. London: Henry Kimpton, 1959. Pp. 242. Figures 13 Price 60*s*.

DURING the every-day practice of anæsthes doctors are accustomed to measure such sim physiological data as the pulse rate, bl pressure and rate of respiration. Facts of thes kinds can be obtained without complicated apparatus and are easily interpreted. Fortunately, they suffice for the production an maintenance of safe anæsthesia for most surgica procedures but, occasionally, either for a particularly complex operation or for an experimental project, they are inadequate. Then, the need to monitor and record these processes more accurately, or indeed to measure others of special value, will mean using complicated instruments. The authors of this excellent book

escribe lucidly the principles and application much of the armamentarium of the clinical hysiologist — cardiotachometry, electro-ncephalography, manometry and blood gas alysis to mention but a small part—in relation the study of anæsthetized patients. This is a st helpful work of particular value to those less than a working knowledge of physics electronics.

Clonal Selection Theory of Acquired Immunity. By SIR MACFARLANE BURNET, M., F.R.S. Nashville, Tennessee: Vanderbilt University Press; London: Cambridge University Press, 1959. Pp. ix nd 209. Figures 12. Price 22*s*. 6*d*.

the lectures which form the substance of book, Sir Macfarlane Burnet has put his most recent theory of antibody n, several essential features of which een derived from ideas suggested by hrlich in his Croonian Lecture of 1899. It is a markable tribute to Ehrlich's genius that his ews should still arouse such interest. Burnet's ain point is that constant heritable mutation of enchymal cells gives rise to a great variety of ividuals distinguishable from each other by a ecific affinity for one out of the large number potential antigenic groupings. Combination an antigen with a cell whose surface has a ecific affinity for one of its antigenic groups lead to several reactions. The most imortant is that in the adult animal it will bilize and stimulate multiplication of that articular cell type. This may in turn lead to ncreased production by the cell, of globulin hich also has a specific affinity for this antiic group, i.e. to antibody production. The ory is elaborated and a variety of pathological onditions such as auto-immunity, allergy and ancer are discussed in these terms.

The author expressly disregards the relevant iochemical data which are available and, itably in a short series of lectures, there is election of the biological evidence. This does ot detract from the interest which this book ll hold for the many medical scientists inated by the problems posed by immunity. he non-specialist, however, should remember hat these lectures are intended to cover only ome aspects of the fields discussed.

The Life and Times of Sir Charles Hastings. By WILLIAM H. MCMENEMEY, D.M., F.R.C.P., D.P.M. Edinburgh: E. & S. Livingstone Ltd., 1959. Pp. xii and 516. Price 50*s*.

THIS book has been prepared with such infinite attention to detail that it is difficult to see the wood for the trees. It tells us much more about the times than the life of Hastings. Indeed, the man is so blurred by the detailed descriptions of meetings that it is almost impossible to make out what kind of a man he was. What is perhaps even more unfortunate is that it is his defects which seem to penetrate most strongly through the haze: his cantankerousness, his resentment of criticism and his ownership of a private mental home which was anything but above criticism.

This is all the more unfortunate as the author has obviously taken tremendous pains over the compilation of what has patently been a labour of love. He will, however, have the consolation of knowing that his painstaking collection of all the available data about the origins of the British Medical Association will be of the greatest value to the student of medical history. It may be arguable whether the Association came into being because of, or in spite of, Hastings, but there can be little doubt that the movement initiated by him in Worcester was the first step towards the political organization of the general practitioners of the country.

NEW EDITIONS

A Synopsis of Obstetrics and Gynæcology, by Aleck W. Bourne, M.B., F.R.C.S., F.R.C.O.G., in its twelfth edition (John Wright & Sons Ltd., 35*s*.) is intended for the student who has read standard textbooks on obstetrics and gynæcology, has listened to lectures and has examined patients. Its object is to refresh his memory by a sufficient display of the facts with which he is presumably already familiar. The factual content is vast; and it is so arranged that the student can quickly discover what gaps in his knowledge require to be filled, the examination candidate may find a scheme for the orderly presentation of his facts, whilst the teacher may consult it to ensure completeness in the preparation of lectures and clinical demonstrations. This new edition has been considerably revised with the addition of new matter (e.g. a chapter on intersex, and many other advances) and a certain amount of dead wood has been removed. The book can confidently be recommended to those for whom it is intended but it will depend upon the attitude of the reader whether he considers the author to have been sufficiently radical in his revision.

Physical Diagnosis, by F. Dennette Adams, M.D., in its fourteenth edition (Baillière, Tindall & Cox Ltd., 96*s*.) remains an excellent book. Its size would daunt the average British student looking for an introduction to clinical medicine. It will be of the greatest value, however, to those doctors who are responsible for initiating the student into clinical medicine by a course

of lectures supplementing the first few months of bed-side teaching. The 23-page summary of electrocardiography is a model of clarity. On the other hand, the student needs a more concise and dogmatic statement of the physical signs in chest disease than is given here.

Surgical Pathology, by Lauren V. Ackerman, M.D., in collaboration with Harvey R. Butcher, Jr., M.D., second edition (Henry Kimpton, £5 12s. 6d.).—Ackerman's textbook of surgical pathology has, in its first edition, already earned the respect of both surgeons and pathologists. The second edition has been extensively re-written in association with Professor Butcher. This is a most impressive book of which perhaps the most outstanding feature is the high quality and interest of its numerous illustrations which in themselves form a fascinating atlas of surgical pathology. The clinical bias of the book is well exemplified by the radiographs and clinical photographs which are of a merit equal to that of the illustrations of gross and micro-scopical pathology. The text is both practical and readable and summarizes opinions which are, in general, in agreement with those held in this country. Of necessity the descriptions of disease are often brief but in each section numerous references are made to the relevant literature in which British authors receive proper recognition.

Special features worth noting are the large chapters on the pathology of skin, eye, vessels and wound healing and the useful information which is given of the value of immediate frozen section and exfoliative cytology. This book will, in the opinion of the reviewer, become a standard work on surgical pathology. Its cost is not excessive when one considers the number (1,114) and quality of the illustrations.

Parasitology, by K. D. Chatterjee, M.D. (K. D. Chatterjee, Rs. 17.50).—The publication of a second edition of this book within fifteen months of its first appearance is a measure of the success which it has enjoyed. The text has been revised and brought up to date and embellished by the addition of 18 further illustrations, 10 in colour. The book, which is well produced and most reasonably priced, covers the whole field of the common protozoa and helminths which affect man. There is no doubt that the author has performed a most useful service to the medical profession in India, where applied parasitology forms such an important part of clinical medi-cine. There is much more to praise than blame in the book, but the reviewer would disagree with the statement that in cerebral malaria parasites are always scanty—in his experience they are extremely numerous. The life-span of *Tænia saginata* is given as 2 to 4 years, whereas it commonly lives for upwards of 10 years. These slips, and a few other of similar character, are minor defects in a work which does much credit to its author.

A Short Textbook of Radiotherapy for Tech-nicians and Students, by J. Walter, B.M., M.R.C.P., F.F.R., D.M.R.E., and H. Miller, PH.D., F.INST.P., in its second edition (J. & A. Churchill Ltd., 56s.) has been expanded to cover important developments which have taken place since the publication of the first edition in 1950, par-ticularly in supervoltage irradiation and radio-active isotopes. Additions include the closely related subjects of hormone therapy and chemotherapy in cancer, together with other technical advances. New data on radiation hazards, a problem of increasing importance, are provided and relevant quotations from 'The Code of Practice for the Protection of Persons Exposed to Ionising Radiations' pub-lished by H.M. Stationery Office in 1957, have been included in place of the old Protection Committee's recommendations. The value of this concise and well-illustrated book has been further enhanced by this edition. It can be recommended not only to student radio-graphers—for whom it has mainly been written—but also to some medical practitioners, other than radiotherapists, whose particular interest may require some basic knowledge of ionizing radiations.

First Studies in Anatomy and Physiology, by John Cairney, D.SC., M.D., F.R.A.C.S., and John Cairney, M.B., CH.B., second edition (Lloyd-Luke, price 30s.).—The fact that this little book first published in 1956 has already run into a re-print and now appears in its second edition is in itself evidence of the good reception which it has been accorded. Primarily written for student nurses, it will also be valuable to student radio-graphers, physiotherapists and other ancillaries. Little alteration has been made in the text, for at this early stage none was required. Most of the changes are minor ones in the sections on hormones and vitamins and in some of the illustrations, bringing up to date a well-written elementary textbook.

The contents of the December issue, which will contain a symposium on 'Diseases of the Ear, Nose and Throat' will be found on page A 154 at the end of the advertise-ment section.

Notes and Preparations see page 669.
Notes from the Continent see page 673.
Fifty Years Ago see page 675.
Motoring Notes see page A 109.
Travel Notes see page A 117.
Bridge Notes see page A 121.

NOTES AND PREPARATIONS

NEW PREPARATIONS

'DIANABOL' tablets each contain 5 mg. of methandrostenolone, and are said to be 'far more specifically anabolic than any other agent' without risk of virilization. The early signs and symptoms of decalcification, such as low backache after the menopause, are said to respond 'dramatically', and other indications include convalescence after operation or severe illness, cachexia of malignant disease, corticosteroid catabolism, and the treatment of underdeveloped children. Available in containers of 25, 100 and 500 tablets. (CIBA Laboratories Ltd., Horsham, Sussex.)

'FUROXONE' preparations contain furazolidone and are intended for the treatment of all forms of gastrointestinal infection, particularly non-specific diarrhœas, bacillary dysentery and bacterial food poisoning. Symptoms are said to clear in most patients within two days of starting treatment. Available as 100-mg. scored tablets in containers of 20 and 200, and as a suspension in 8-ounce bottles, containing 100 mg. in each 'medical tablespoonful'. (Smith Kline & French Laboratories Ltd., Welwyn Garden City, Herts.)

'NARDIL' tablets each contain 15 mg. of phenelzine dihydrogen sulphate and are intended for use in depressive states 'whether they occur in the younger, middle or older age-groups, alone or in conjunction with other psychiatric disorders'. Improvement is said to occur usually within ten days of starting treatment, and side-effects are said to be minimal. Available in bottles of 100 and 500 sugar-coated tablets. (William R. Warner & Co. Ltd., Eastleigh, Hampshire.)

'ORISULF' tablets each contain 0.5 g. of 1-phenyl-5-sulphanilamidopyrazole and are intended for the treatment and prophylaxis of upper respiratory and urinary-tract infections. They are said to have a rapid and prolonged antibacterial effect and to be safe and well tolerated. Available in containers of 25, 100 and 500 tablets, and also as a suspension in bottles of 50 ml., containing 0.5 g. in each teaspoonful. (CIBA Laboratories Ltd., Horsham, Sussex.)

'PRIPSEN' granules contain piperazine phosphate and standardized senna ('senokot') and are intended for the treatment of threadworms and roundworms. Each teaspoonful of granules (2.6 g.) contains 1 g. of piperazine phosphate B.P. and 200 mg. of senna pod B.P. in a palatable base. A single dose of 'pripsen' is said to give a cure rate for threadworms 'as high as that previously obtained with the usual seven-day treatment'. The same single dose is said also to be effective for roundworms. Available in tubes of 10.4 g. (one full dose) and in containers of 454 g. (Westminster Laboratories Ltd., Chalcot Road, London, N.W.1.)

'PRO-BANTHINE WITH DARTALAN' tablets each contain 15 mg. of propantheline bromide ('probanthine') and 3 mg. of thiopropazate dihydrochloride ('dartalan'). They are intended for 'the control of stress and to relieve distress in organic and functional disorders of the gastro-intestinal tract'. They are contraindicated in patients with glaucoma, and should be used with caution in patients with prostatic enlargement and with 'true pyloric stenosis'. Side-effects are said to be 'rare'; they include hypotension, blurring of vision and constipation. Available as peach-coloured, compression-coated tablets in bottles of 50, 100, and 500. (G. D. Searle & Co. Ltd., Lane End Road, High Wycombe, Bucks.)

'TRASYLOL' contains the inactivator of the pancreatic hormone, kallikrein; it also inhibits the activity of trypsin. Supplied in 2-ml. ampoules, each containing 2000 kallikrein inactivator units, for drip infusion or slow intravenous injection. 'Extensive clinical trials' have shown it to be of value in the treatment of acute and chronic pancreatitis. There are said to be no known complications. Available in boxes of 5 ampoules, and hospital packings of 25 ampoules. (FBA Pharmaceuticals Ltd., 37-41 Bedford Row, London, W.C.1.)

PHARMACEUTICAL NOTES

AMES COMPANY announce that 'altest' reagent tablets are no longer available. This tablet test has been superseded by 'albustix' reagent strips for the detection of protein in urine.

C. L. BENCARD LTD. announce that the name of their company has now been changed to BEECHAM RESEARCH LABORATORIES LTD., and their address is: Great West Road, Brentford, Middlesex. The Bencard allergy preparations will continue to be supplied under their old name, and a Bencard Allergy Division of the new company has been formed at the same address.

FBA PHARMACEUTICALS LTD. announce that future orders for 'glumorin' tablets will be met with 30 b.u. tablets, as the 10 b.u. tablets are being withdrawn from the market. (37-41 Bedford Row, London, W.C.1.)

MARMITE LTD. announce that 'salt-free Marmite,' which has been supplied to hospitals under the name of 'unsalted yeast extract,' is now generally available. Supplied in jars of 4 and 8 ounces. (Walsingham House, Seething Lane, London, E.C.3).

FILM NEWS

La Presse Médicale announce that the 'annual prize for medico-surgical cinema', comprising 100,000 Fr. (which may be divided) and various other prizes, will be awarded during the last session of the course of 'Actualités médico-chirurgicales' to be held in Paris in April 1960. Any 16-mm. film may be submitted, and the latest date for entries is February 29, 1960. Full details may be obtained from the Secretariat, La Presse Médicale, 120 Boulevard Saint-Germain, Paris VI^{e}, France.

PRIZES

THE *American College of Chest Physicians* is offering three cash prizes for the best essays by undergraduate medical students on any phase of the diagnosis and treatment of chest diseases (cardiovascular or pulmonary). The first prize in the 1959 competition was awarded to Michael A. Salmon of the Middlesex Hospital Medical School, for his essay entitled 'Pulmonary hydatidosis, a review'. Entries must be submitted by April 1, 1960, and full details may be obtained from the American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois, U.S.A.

CHRISTMAS GIFTS FUND APPEAL

SIR HENRY TIDY, President of the Royal Medical Benevolent Fund, writes: 'To receive a gift at Christmas time is a joy to everyone, but particularly to those who are lonely or in need. To none is a gift more welcome than to those who have fallen on hard times. Our beneficiaries include colleagues who have met with misfortune, and widows and children who are often in desperate need when their breadwinner has been taken before he has been able to make provision for them. A gift at Christmas will enable them to enjoy some of the traditional good cheer of the season'. Contributions, marked 'Christmas Gifts', should be sent to the Royal Medical Benevolent Fund, 37 St. George's Road, Wimbledon, London, S.W.19.

CHRISTMAS CARDS AND SEALS

Chest and Heart Association.—This year's Christmas seals issued by the Chest and Heart Association depict British birds. The seals are printed in gay colours and are available in sheets of 60, price 5*s.*, from the Duchess of Portland, D.B.E., The Chest and Heart Association, Tavistock Square, London, W.C.1.

Imperial Cancer Research Fund.—To help in raising the £1,000,000 which is needed to build and equip new laboratories which will be the most advanced cancer research centre in Europe, Miss Anna Zinkeisen has permitted the reproduction of five of her paintings and drawings to be sold as Christmas cards for the benefit of the Imperial Cancer Research Fund.

The one illustrated here, 'Madonna and Christ-child', will be printed in blue and costs 10*s.* 6*d.* a dozen, and the others are entitled 'The maternity sister' (21*s.* a dozen), 'Flowers'(16*s.* a dozen), 'The picnic' (16*s.* a dozen), and 'Solitude' (9*s.* a dozen). Imperial Cancer Research Fund, Lincoln's Inn Fields, London, W.C.2.

National Deaf Children's Society.—This year's Christmas card issued by the National Deaf Children's Society depicts the Christ Child wrapped in swaddling clothes and playing with a pair of robins. It is reproduced in pale blue and red and is available (3*s.* 6*d.* for six cards) from the Secretary, The National Deaf Children's Society, 1 Macklin Street, Drury Lane, London, W.C.2.

PHOTOGRAPHIC BIBLIOGRAPHY SERVICE

A BIBLIOGRAPHY of original articles on photographic techniques and on photographic applications in the medical and biological sciences has now been established by the Medical Group of

The Royal Photographic Society of Great Britain. This consists of punch cards, each of which carries an abstract of an original article. Almost four hundred new cards are added annually to the existing total of well over two thousand such classified abstracts. The honorary librarian of the group is therefore able to quote the references of papers which have a bearing on any problem concerned with photography in medicine or biology. This service is extended, free of charge, to all *bona fide* inquirers. Detailed requests for references to the literature should be addressed to: J. A. Fairfax-Fozzard, M.A., F.R.P.S., The School of Anatomy, The University, Cambridge.

HOMES FOR FOREIGN STUDENTS

At any one time there are more than 40,000 students from abroad in Britain, over half of whom are in the London area. Many of them are entitled to call on the British Council for help in finding lodgings. In addition, a certain number of officials and other senior visitors, who come to this country for periods of one to six months, prefer to live in private houses as paying guests rather than in hotels. The British Council urgently needs to increase its list of landladies who will provide such accommodation not too far from central London, or close to local technical colleges. Anyone who has a spare room and would like to consider the possibility of taking an overseas student or a senior visitor is therefore asked to get in touch with the London Overseas Students Department, British Council, 65 Davies Street, London, W.1 (Tel. GROsvenor 8011).

ROYAL MEDICAL BENEVOLENT FUND

The recently published annual report of the Royal Medical Benevolent Fund for 1958 announces that the homes for 'indigent doctors' provided by a bequest from the late Mr. J. T. M. Giffen, F.R.C.S., are now open. They consist of a house in Putney which has been converted into five self-contained flats, each consisting of a bedroom, sitting-room, bathroom and kitchen; there is also a pleasant garden. The flats are rent free, but a small charge is made to the residents as a contribution towards maintenance. The purpose of these flats is that retired doctors and their wives 'can be assured of a pleasant home in which to pass the evening of their lives while preserving that feeling of independence so dear to the heart of the professional man'.

The committee of the Fund will be grateful if readers will recommend applicants for residence, or bring these flats to the notice of suitable retired married doctors. The address of the Fund is 37 St. George's Road, Wimbledon, London, S.W.19.

THE WELLCOME TRUST

Grants totalling over £400,000 were made by the Wellcome Trust during the year ended August 31, 1959. Among the more unusual ones in this country were £3,600 to the Society of Apothecaries to establish a research fellowship in the history of medicine and pharmacy, £2000 to the Society for the Study of Fertility to establish a *Journal of Reproduction and Fertility*, and £2000 to assist British workers to attend the 21st International Physiological Conference at Buenos Aires. Cambridge University came off best, with two grants totalling £180,000. Among grants made outside this country, were £12,500 to the physiology department of Makerere College, Uganda, to provide a mobile laboratory and animal house, and £13,000 to the department of physiology at McGill University, Montreal, to provide an electron microscope.

GROUP PRACTICE LOANS

Hitherto the Group Practice Loans Committee of the Ministry of Health has never considered that they should reject an application for a loan solely on the grounds that the work of building or converting premises had already been started or finished at the time of application for the loan. As from January 1, 1960, however, the committee will not normally grant a loan if the application is first made after the work in respect of which the loan is requested has advanced beyond the preliminary stages of planning and the work of building or conversion has begun or been completed. Any group therefore which is proposing to seek a loan in respect of a project which is already under way, or will be started before the end of 1959, should make application before January 1, 1960.

NEW RESEARCH INSTITUTE

A new biological research institute, built and equipped at a cost of £750,000, has recently been opened in Nottingham by Boots Pure Drug Co. Ltd. The seven-storey building has 24 laboratories and, in addition, it houses the company's scientific library of 25,000 volumes —believed to be the largest owned by any pharmaceutical company in Great Britain.

THE COLOUR OF THE IRIS AND SENSITIVITY TO PAIN

In Australians of European stock an association between the colour of the eyes and the reaction to pain resulting from dental cavity preparation is reported by P. R. N. Sutton (*Nature* (*Lond.*), 1959, **184**, 122). His report is based upon his findings in 403 consecutive subjects whose teeth were being prepared for filling. None of the blue-eyed subjects required a local anæsthetic for this purpose, compared with 2% of those

with greyish-blue or greenish-grey eyes, 30% of those with light brown or brown eyes, and more than 53% of those with dark brown eyes.

A NEW MEDICAL STAMP

A NEW postage stamp in the 'Famous Americans' series is to be issued in the United States in December to commemorate the 150th anniversary of the successful ovariectomy performed by Dr. Ephraim McDowell on Christmas Day 1809—which has been described as the 'world's first successful scientific abdominal operation'.

PUBLICATIONS

Childbirth Without Pain, by Dr. Pierre Vellay *et al.*, translated by Denise Lloyd, is the latest in the series which has been published in France, describing the psychoprophylactic method of preparation for childbirth. This is a method that has achieved considerable support in Continental centres, and although it has much in common with the Dick Read method it differs in certain vital and fundamental aspects. The lectures which the woman receives are extremely thorough and well-conceived. The physiology and psychology of normal pregnancy and labour are discussed in considerable detail. The physiology of pain is also discussed quite fully. The patient is encouraged to take an active interest in her labour and at no point is there a suggestion that she is 'escaping' and very little, if any, analgesia is ever given when this method is adopted. The book describes the technique in considerable detail and will be valuable for mothers to read themselves in centres where this method is adopted. It does require a certain level of intelligence, however, to appreciate all that is described and certainly this method is most effective in women of social grades 1 and 2. (Hutchinson & Co. (Publishers) Ltd., price 35*s.*)

The Catarrhal Child.—This well-produced, well-printed pamphlet of 40 pages is introduced by Dr. Stanley Graham who questions the validity of the title if it is taken to suggest the existence of a diathesis: 'To me this conception has little to commend it'. The seven contributors to the symposium cover various aspects of the subject: incidence, bacteriology and treatment. Dr. Richard Dobbs presents three valuable surveys. The reader is left with no great impression of new ground broken in this stubborn field. (The Chest and Heart Association, price 6*s.*)

Expert Committee on Respiratory Virus Diseases, First Report, WHO Technical Report Series No. 170, provides a useful summary of one of the most rapidly expanding fields of medicine. The chairman of the committee is Dr. C. H. Andrewes. (H.M. Stationery Office, price 3*s.* 6*d.*)

Never Say Die: A Return to Everyday Living for the Partly Disabled, by Anthony Richardson. —The author suffered a severe hemiplegia and after a period in hospital returned to his lodgings determined to manage for himself. So he has learnt to wash and dress, to tie his tie in as neat a knot as anyone could wish, to eat his food 'like a gentleman', and to be as little trouble as possible. How was it done? He describes some of his techniques in close and helpful detail. In every operation, a plan must be made and every movement must be foreseen; an appropriate drill must be devised and used until it becomes instinctive habit. (Max Parrish & Co. Ltd., price 12*s.* 6*d.*)

Christ and Freud, by Arthur Guirdham, M.A., D.M., D.P.M., compares the demands that the psychoneurotic makes from his ivory tower of acute self-awareness with what western theology and Freudian psychoanalysis offer him. He finds that sermonizing him and analysing him are unlikely to satisfy his inner needs, and on the assumption that neurotic disorder is far less common in the East, supports Aldous Huxley's plea for Western Man to seek more and more detachment, in place of pursuing so ardently a success story. Dr. Guirdham is always stimulating even when he is so provocative. If one can see many questions that he fails to answer, his tilting at clerics, at Freudians, the National Health Service, and many other false gods, as he would call them, makes for pleasant reading, for the thesis has many delightful asides and quotations. (George Allen & Unwin Ltd., price 21*s.*)

The Pony Club Book No. 10.—The 1959 issue of this popular 'annual' contains an article by Mrs. N. W. Jacques ('Help from the Horse') on the use of pony-riding as a means of rehabilitation for paralysed children, especially those with poliomyelitis. It gives an admirable description of this increasingly popular method of helping the crippled child. There is also a fascinating description by Miss Joyce Stephens of her experiences as a member of the world-famous Kentucky Frontier Nursing Service. (The Naldrett Press Ltd., price 15*s.*).

CORRIGENDA.—In the article on 'Cough Suppressants' in our September issue, the manufacturers of 'brovon inhalant' should have been given as Moore Medicinal Products Ltd. (pp. 348-349), and the antihistamine constituent of 'thorpax' should have been given as isothipendyl (p. 350). Ward, Blenkinsop & Co. Ltd. inform us that since November 1958 codeine has been omitted from 'pavacol syrup' when it was replaced by pholcodine (p. 350).

NOTES FROM THE CONTINENT

A European Newsletter

FRANCE

Barbiturate poisoning.—In a report from the resuscitation centre of the Claude Bernard Hospital, Paris, Professor P. Mollaret and his colleagues, as a result of animal experiments and their subsequent experience with 58 patients, commend the alkalinization of the blood as a useful ancillary measure in the treatment of barbiturate poisoning. The rationale of this form of therapy is that, as demonstrated in the experimental animal, the alteration in the pH of the blood, produced by the administration of large doses of alkali, inhibits the penetration of the barbiturate into the blood cells, thereby increasing the plasma concentration of the barbiturate. This, in turn, increases the rate of elimination through the kidneys, and so allows the body to get rid of the ingested barbiturate in a shorter period of time. Their experience in patients would appear to confirm the validity of this thesis. In the clinical use of this form of therapy two points are stressed by the authors. The first is that it is merely ancillary to other well-recognized methods of treatment such as stimulation of the respiratory centre. The second is that this form of treatment can only be used in the presence of adequate renal function—to ensure the urinary excretion of the raised plasma barbiturate concentration—and a systolic blood pressure that does not fall below 100 mm. Hg.

The method of alkalinization depends upon whether or not the patient has required intubation or tracheotomy. If neither of these has been necessary, alkalinization is carried out by giving an intravenous infusion of isotonic sodium bicarbonate (14 g. per litre). The average volume administered in twenty-four hours was 3 to 4 litres, although in some cases as much as 6 litres was given. In the case of intubated patients, or those who have required a tracheotomy, a hypertonic sodium bicarbonate solution (30 g. per litre) is used. The total amount given in the twenty-four hours is 0.5 to 1 litre. The hypertonic solution is supplied in bottles containing 250 ml., and the method of administration is to alternate these with equal volumes of the isotonic solution so that the total volume of fluid given in the twenty-four hours is 4 litres. The reason why the hypertonic solution is only used in patients who have been intubated or have had a tracheotomy is that it is liable to depress the respiratory centre, which can be easily countered by endotracheal insufflation. An incidental, but useful, advantage is that in these patients it is also possible to induce hyperventilation, thereby increasing the pH of the plasma still further and so increasing the rate of excretion of the barbiturate.

It is claimed that using this method of therapy, not only did all the patients recover, but the duration of coma was considerably reduced.

An oxytocin aerosol.—The possibility of administering oxytocin in the form of an aerosol has been investigated at the department of obstetrics in the University of Lyons. In a preliminary report A. Notter reports that the administration of 10 or 15 units of oxytocin as an aerosol over a period of a quarter of an hour produced a satisfactory response in six primiparæ and 14 multiparæ. The clinical response was confirmed by tensiometric recordings. No adverse effect was noted in either the mother or the babies. It is suggested that better and more consistent results could be obtained if a more consistent particle size—less than 0.5μ in diameter—were available. The possible use of an oxytocin aerosol is considered to be in the initial stages of labour, particularly in the presence of inadequate dilatation of the cervix.

The pathology and treatment of senile osteopathies.—In the majority of cases, according to Professor A. Lichtwitz and his colleagues, the senile osteopathies are associated with changes in the organic structure of the bones: i.e. osteoporosis. On the other hand, whilst they are seldom due solely to a deficiency of phosphorus and calcium (i.e. osteomalacia), in many cases there is a combination of osteoporosis and osteomalacia. Calcium deficiencies, which often pass unnoticed when associated with osteoporosis, are said to be the result of two processes that are usually unrecognized in the aged: renal glomerular in-

sufficiency without nitrogen retention, and a diminished output of chlorides. The scheme of treatment suggested for the treatment of these senile osteopathies includes a high-protein intake and the administration of the so-called non-virilizing androgens in the form of one of the nor-testosterone derivatives. In resistant cases, it is suggested that 'massive' doses of œstrogens might be tried, as well as stimulation of the parathyroid glands by means of sudden stoppage of calcium combined with the administration of sodium phytate.

GERMANY

Trypsin in ophthalmology.—Satisfactory results are reported by H. Hofmann and his colleagues from the use of zonulolysis with trypsin in the treatment of cataract. The zonulolytic action of trypsin is said to be about three times as strong as that of alpha-chymotrypsin. The strength of trypsin used was 0.1 mg. per ml. No side-effects have been noted as yet, nor has there been any evidence of inactivation of trypsin by the aqueous humour.

'*Pupillary lenses*'.—A new type of artificial lens to which he has given the name of a 'pupillary lens' is commended by C. D. Binkhorst. This lens is said to have all the advantages of an anterior chamber lens, without any risk of subluxation, or retinal damage. The new lens is independent of the depth of the anterior chamber, thereby removing the difficulty of estimating the correct length of the lens, which is necessary in the case of anterior chamber lenses. A further advantage claimed for the pupillary lens is that it can be implanted in the growing eye. Its focusing is dependent on the sphincter of the iris and is therefore said to be more accurate than that of any other artificial lens. Besides being self-focusing, it is more physiological than the anterior chamber lens in that it is farther from the retina.

Intravenous fat infusions.—Now that a stable emulsion of fat is available for intravenous infusion, R. Dohrmann and his colleagues have studied its effect upon the serum lipids and serum lipoproteins in patients. After four hours' infusion there was as a rule no change in the total serum lipid concentration and little, if any, alteration in the 'lipid spectrum'. After eight hours' infusion, however, there was usually a marked increase in the total lipids. In every case there was an increase in the neutral fats and a marked decrease in the serum cholesterol. The view is expressed that, together with infusions containing glucose and amino-acids, the new fat infusion should prove a definite advance in parenteral feeding—particularly in surgery.

Artificial insemination.—The recent German doctors' congress at Lübeck passed a unanimous resolution strongly condemning artificial insemination outside marriage. The view was expressed that it is impossible to foretell the medical, legal and psychological results of A.I.D., and that therefore no doctor was justified in accepting responsibility for being a party to it. Particular concern was expressed at the suggestion of instituting 'semen banks' such as are being established in the United States of America.

The radio doctor.—Primarily to cope with the increasing number of road accidents, an emergency radio service has been installed in Hamburg. The doctors' panel in Hamburg has acquired a radio transmitter which is used by the member of the panel who is on call—or the duty doctor as he is known. The transmitter is portable and can be used in any car. By its means the doctor can be contacted by the police at any time and no matter where he is. Whilst the scheme was instituted originally to deal with road accidents, it is proving equally valuable for other emergencies such as attempted suicides.

'*Notes from the Continent*' *are produced in collaboration with the Editors of* Bruxelles-Médical (*Belgium*), Le Concours Médical (*France*), Münchener Medizinische Wochenschrift (*Germany*), *and* Minerva Medica (*Italy*).

THE PRACTITIONER

Fifty Years Ago

'Dead driftwood floats where argosies were drowned. The best is secret from the world's applause. See! gleaners come, with eyes upon the ground, After Oblivion's harvest, picking straws'.
Laurence Binyon, *History*

NOVEMBER 1909

WILLIAM B. COLEY, M.D., Professor of Clinical Surgery to Cornell University Medical School, New York, begins the first article in this number, 'The Treatment of Inoperable Sarcoma by Bacterial Toxins (the Mixed Toxins of the Streptococcus of Erysipelas and the Bacillus Prodigiosus)': 'The subject of the treatment of sarcoma with the mixed toxins of erysipelas and bacillus prodigiosus is one upon which I have been working constantly for the last seventeen years, and one which has grown more interesting to me with each succeeding year. While the results have not been as satisfactory as one who is seeking perfection could wish, they have been sufficiently real and tangible, I think, to be entitled to more careful consideration than they have yet received. Furthermore, they may have an important bearing upon the whole cancer problem, since, if by the administration of certain bacterial toxins we can cause the degeneration, death, and absorption of living tumour cells of one variety of cancer, sarcoma, it is not unreasonable to suppose that by the use of some other forms of bacterial toxins, we may succeed in destroying or inhibiting the growth of the other and more common variety, carcinoma'.

Samuel James Crowe, A.B., M.D.
(1883-1955)

John Cowan, M.D., D.Sc., Professor of Medicine, Anderson's College Medical School, Glasgow, discussing 'The Current Theories Regarding Arterio-Sclerosis: The Symptoms', writes: 'The recent introduction into clinical methods of the Riva-Rocci sphygmomanometer and its numerous modifications has put within the reach of the practitioner a method by which the arterial pressure may be measured with fair accuracy and without any special difficulty of technique. But, while it is useful to have figures which can be contrasted, a measure in some way of the severity of the disturbance, it must be remembered that the blood pressure varies to a considerable extent in the healthy individual from causes of a temporary and often trivial nature. . . . The information which is desired can, too, be obtained from other data. Digital examination of the pulse is at the present day too much depreciated. . . . The sphygmomanometer, too, gives no information with regard to the condition of the arterial walls, information which is readily afforded by the finger'. This interesting article concludes: 'Arterio-sclerosis is no new disease. It is "plethora"; it is often "renal inadequacy"; it is often "senile heart"; it is often "gout of the aberrant type", and the "uric acid diathesis". In many cases it is "old age", which is but rarely the wearing out of undamaged tissues, and too generally the result of physiological misbehaviour in the past: misbehaviour which leaves its first marks upon the arteries'.

In 'Notes on Rheumatic Heart Disease in Children', J. Walter Carr, M.D., F.R.C.P., Senior Physician to the Victoria Hospital for Children, states that 'of all the children of five years old and upwards admitted, in three different years, to the medical wards of the Victoria Hospital for Children, Chelsea, nearly 50 per cent. were suffering either from rheu-

matic fever, from chorea, or from heart disease (not congenital), that is to say, from rheumatism or its consequences. Of the boys about 40 per cent., and of the girls nearly 58 per cent., were rheumatic'.

Some graphic passages occur in the article 'Acute Peritonitis' by E. Stanmore Bishop, F.R.C.S., Hon. Surgeon, Ancoats Hospital, Manchester: 'The face is that of a "hunted" person. It is usually said to express "anxiety", but it is far more than that. There is the same piteous appeal for help and the same expression of hopelessness as to obtaining it as is seen in an animal at bay after a long hunt. The sufferer scans the faces of those around, but appears to find nothing there to which he can cling for safety. He feels in imminent danger and knows not how to evade it'.

H. Campbell Thomson, M.D., F.R.C.P., Physician to the Hospital for Epilepsy and Paralysis, Maida Vale, surveying 'Some Recent Literature on Diseases of the Nervous System', refers to 'an important article' in the *Johns Hopkins Hospital Bulletin* of April, 1909, by S. J. Crowe on the therapeutic value of urotropin in meningitis: 'The author concludes (1) that urotropin when given by the mouth invariably appears in the cerebrospinal fluid. (2) The largest amount . . . is present . . . from 30 to 60 minutes after the drug has been given. (3) After doses of urotropin within therapeutic limits a sufficient amount . . . appears in the cerebrospinal fluid to exercise a decided inhibitory effect on the growth of organisms inoculated into this fluid after its removal from the body. (4) Following a subdural inoculation of dogs and rabbits, with streptococcus, 60 to 80 grs. a day . . . will markedly defer, and in some cases prevent, the onset of a fatal meningitis. (5) . . . The prompt administration of urotropin is advised in all clinical cases in which meningitis is a possible or threatened complication, or even when meningeal infection has actually occurred'.

Samuel James Crowe (1883-1955) graduated M.D. at Johns Hopkins in 1908 and in 1912 was asked by W. S. Halsted to organize and head a division of otolaryngology. He subsequently was appointed professor of laryngology and otology in the university and became an internationally known authority on deafness. Taciturn and shy, he was beloved of his students, colleagues, and patients.

The books reviewed this month include 'A Synopsis of Surgery' by Ernest W. Hey Groves ('Such a book as this, in which the matter is methodically arranged, and the essentials of diagnosis and treatment are concisely given, may well play the part of an opsonin'.).

W. R. B.

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